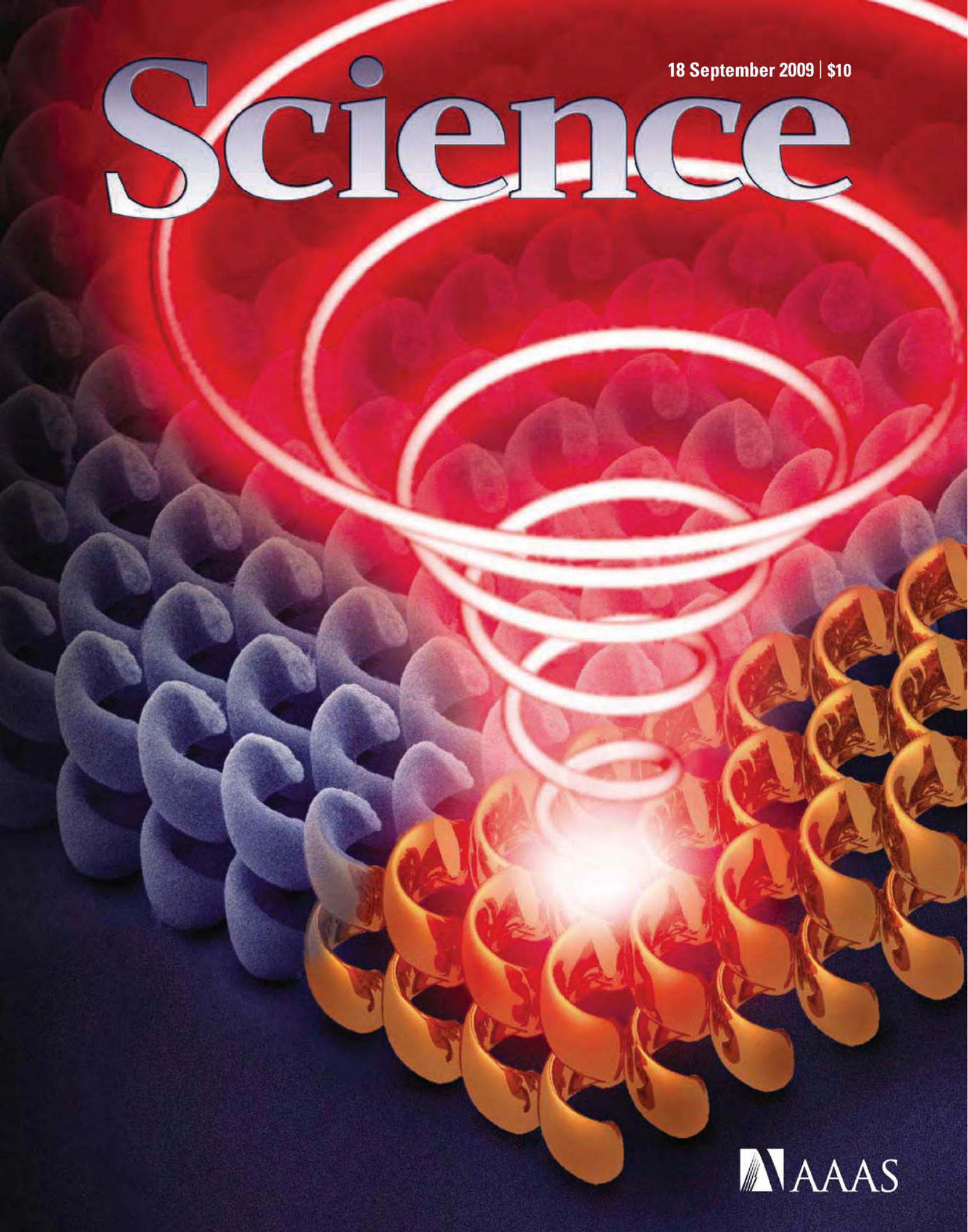


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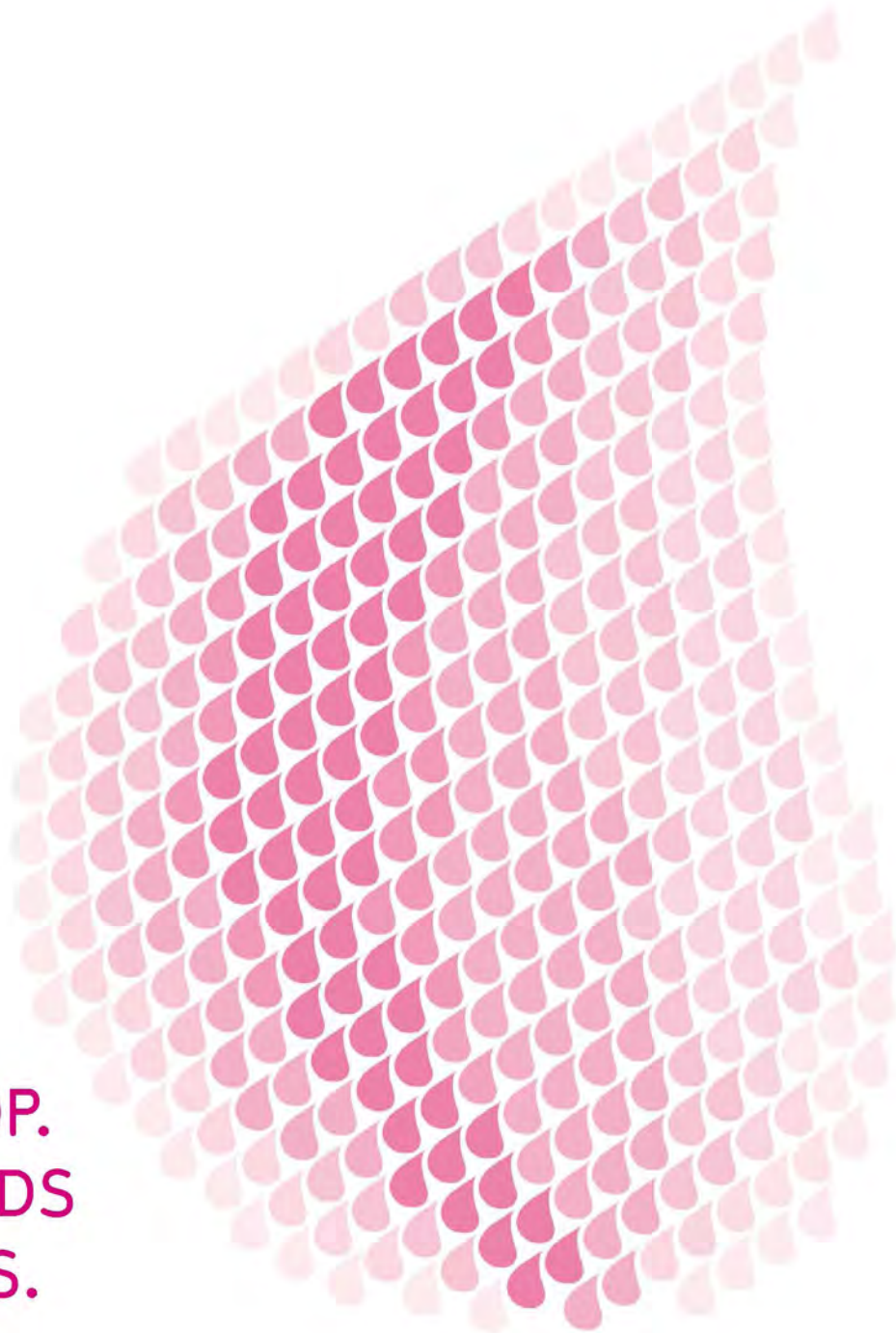
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process developers what they
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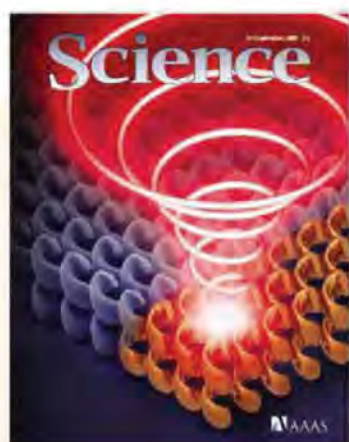
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COVER

Scheme of a photonic metamaterial composed of three-dimensional gold helices, each about 1.4 micrometers in diameter, fading to an oblique-view electron micrograph of the helices as fabricated (blue). The illuminated spiral symbolizes circularly polarized light impinging on the chiral metamaterial. The structure works as a circular polarizer for a frequency range exceeding one octave. See page 1513.

Illustration: Michael S. Rill (structure fabrication by Justyna K. Gansel and Michael Thiel)

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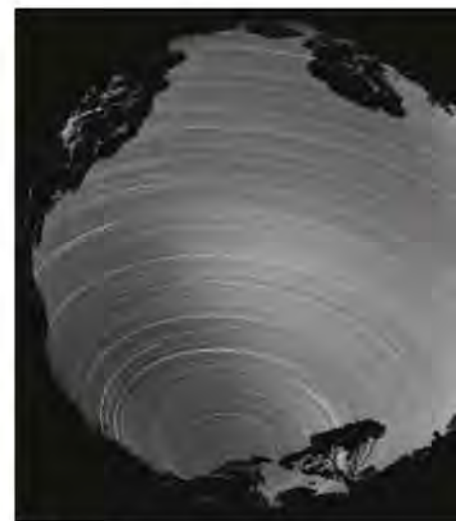
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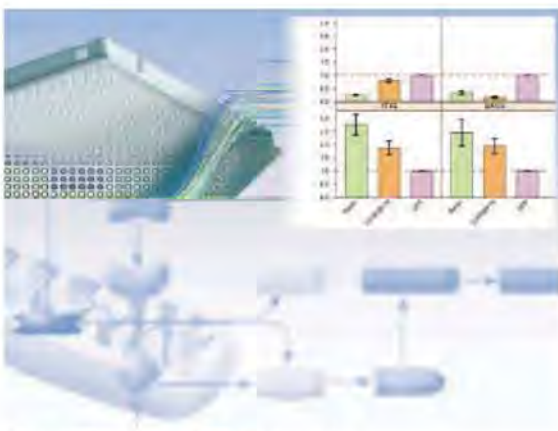
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P. C. Sereno et al.

The distinct features of *Tyrannosaurs*, such as their large skull and tiny arms, appear in an earlier small-bodied species.
10.1126/science.1177428

Three-Color Entanglement

A. S. Coelho et al.

Three bright light beams of different colors can be entangled.
10.1126/science.1178683

Control of Iron Homeostasis by an Iron-Regulated Ubiquitin Ligase

A. A. Vashisht et al.

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An E3 Ligase Possessing an Iron-Responsive Hemerythrin Domain Is a Regulator of Iron Homeostasis

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Comment on "The Dynamic Control of Kiss-And-Run and Vesicular Reuse Probed with Single Nanoparticles"

B. Granseth et al.

full text at www.sciencemag.org/cgi/content/full/325/5947/1499-b

Response to Comment on "The Dynamic Control of Kiss-And-Run and Vesicular Reuse Probed with Single Nanoparticles"

Q. Zhang et al.

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H. P. Makarenkova et al.

Manipulation of the interaction of a morphogen with the extracellular matrix changes its biological activities by altering its diffusion.

RESEARCH ARTICLE: Tks5-Dependent, Nox-Mediated Generation of Reactive Oxygen Species Is Necessary for Invadopodia Formation

B. Diaz et al.

RESEARCH ARTICLE: Novel p47^{phox}-Related Organizers Regulate Localized NADPH Oxidase 1 (Nox1) Activity

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PERSPECTIVE: Regulation of Cancer Invasion by Reactive Oxygen Species and Tks Family Scaffold Proteins

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PERSPECTIVE: Endocannabinoids Can Open the Pain Gate

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A History of Beginnings

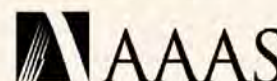
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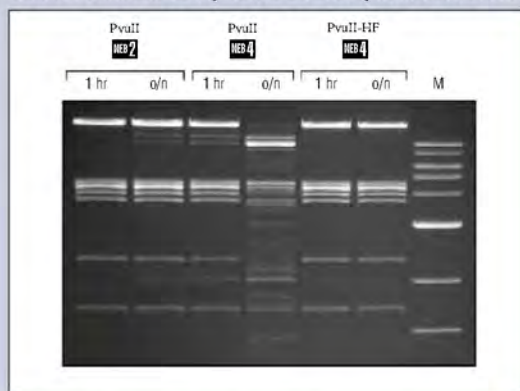
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<< Monitoring Massive Microbial Dispersal

Quantifying the relative influence of present-day environmental conditions and geological history on the spatial distribution of species represents a major challenge in microbial ecology. Ecological approaches to distinguish between these two biogeographic controls are limited by environmental variability both in space and through time (see the Perspective by **Patterson**). Using a 1.5-million-year fossil record of marine diatoms, **Cermeño and Falkowski** (p. 1539) show that, even at the largest (global) spatial scale, the dispersal of marine diatoms is not very limited. Environmental factors are the primary control shaping the global biogeography of marine diatom morphospecies. Thermophilic microorganisms are routinely detected in permanently cold environments from deep sea sediments to polar soils. **Hubert et al.** (p. 1541) provide a quantitative analysis of a potentially large-scale dispersion of thermophilic bacteria in the ocean. Approximately 10^8 thermophilic spores are deposited each year on every square meter of Arctic sediment.

Corkscrew Polarizer

Strong optical activity, measured in terms of a material's ability to polarize light, usually requires a material several hundred wavelengths thick.

Gansel et al. (p. 1513, published online 20 August; see the cover) show that the tunable electromagnetic response of metamaterials may offer a route to reduce the amount of material required for strongly optically active materials. Based on the standard metamaterials design of the splitting resonator, photolithography was used to define an array of three-dimensional gold nanocorkscrews. Just a single wavelength thickness of the corkscrew design was required for a circular polarizer operating over an octave of bandwidth.

Cold Atom Magnetism

Magnetic ordering arises from the strong interactions between atoms, with its origins deeply rooted in quantum mechanics. How the ordering comes about, however, has long been a topic of debate because most condensed-matter systems are limited by a somewhat fixed parameter space. Cold atom systems, by comparison, provide the

ability to tune the magnitude and sign of the atom-atom interaction, as well as the density.

Jo et al. (p. 1521; see the Perspective by **Zwenger**) exploit this flexibility to use an ensemble of ultracold fermionic atoms as a "quantum simulator" to explore the possibility of magnetic ordering. As the repulsive interaction between atoms is increased, an instability occurs in the free two-component Fermi gas (or jellium), which results in a phase transition and the ferromagnetic ordering of the atoms.

The Meteorite Who Fell to Earth

Orbital data is available for only a handful of meteorites. Some are found long after they fell to Earth. Others are recovered after they have been observed falling through the atmosphere, but their trajectories are rarely recorded. **Bland et al.** (p. 1525) used a photographic camera network located in the Australian desert to track a fireball in the sky, find the meteorite, and establish its orbit. The meteorite is a basaltic

achondrite; most such rocks have been traced to the major asteroid Vesta. In this case, the meteorite's isotopic composition and orbital properties suggest a distinct parent asteroid—a different source of basaltic material residing in the innermost main belt.

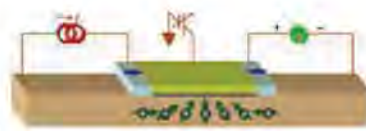
Predicting Terrorism?

Terrorists may be extremists whose opinions do not reflect the mainstream views in their country. Alternatively, public opinion could provide a useful indicator of the likelihood of terrorism.

Krueger and Malečková (p. 1534) used data from the Gallup World Poll of public opinion and the National Counter Terrorism Center to demonstrate a positive relationship between the percentage of people in a country who disapprove of the leadership of another country and the number of terrorist attacks carried out by people or groups from the former country against the latter. Although the data do not demonstrate causality, they do suggest that public opinion can provide an "early warning signal" of future terrorist threats.

Transistors Switch onto Spin

Using the spin of an electron in addition to, or instead of, the charge properties is believed to have many benefits in terms of speed, power-cost, and integration density over conventional electronic circuits. At the heart of the field of spintronics has been a proposed spin-analog of the electronic transistor, the spin field effect transistor. **Koo et al.**



(p. 1515) demonstrate the injection and detection of spin between two ferromagnetic contacts and show how the magnitude of the spin-current between the source and drain contacts can be controlled by a voltage applied to a gate. The results present an experimental realization of the concepts described for the spin-transistor.

Oblique Reasoning

In Milankovich theory, the canonical theory of glaciation and deglaciation, ice sheets wax and wane in response to the amount of summer insolation at a latitude of 65°N , which is consistent with the observed timing of the last deglaciation.

Continued on page 1473

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The penultimate glaciation behaved quite differently, however. Now, **Drysdale et al.** (p. 1527, published online 13 August) offer firmer constraints on the timing of the penultimate deglaciation, by correlating a difficult-to-date marine record of ocean volume to a precisely datable nearby speleothem (terrestrial stalagmite). Ocean volume began to increase about 141,000 years ago, thousands of years before the rise in 65°N summer insolation. Thus, instead of the forcing mechanism proposed by Milankovich, variations in Earth's obliquity may be mostly responsible for the disappearance of ice sheets.

Now Shown in 3D

With the advent of systems-wide technologies and the development of analytical methods, data produced by analyzing individual or small groups of molecular components can be integrated to reassemble whole biological systems. **Zhang et al.** (p. 1544) have undertaken a major technological challenge: to integrate biochemical data with experimentally determined or predicted three-dimensional structures of all proteins involved in the central metabolism of a bacterial cell. This integration of large-scale data sets provides evolutionary and functional insights and furthers our understanding of the molecular assembly of complex biological networks.

A Separate System for Itch Processing

It has been a long-standing question if itch is a subquality of pain involving the same neuronal elements or if distinct, so-called labeled lines exist in the nervous system for both sensations. To address this question directly, **Sun et al.** (p. 1531, published online 6 August) destroyed neurons in the superficial spinal dorsal horn that express the gastrin-releasing peptide receptor. This receptor is known to be involved in mediating itch but not pain sensations. In various animal models, ablation of gastrin-releasing peptide



receptor-expressing spinal dorsal horn neurons reduced itch without changing pain perception. Thus, itch and pain indeed appear to be mediated by distinct labeled lines in the central nervous system.

Locust Wing Aerodynamics

Insect wings function as deformable aerofoils, but the precise aerodynamic benefits of the observed deformations have remained obscure. Previous models have treated the wing as a flat plate, lacking any deformation, even though it is clear that the locust wing can twist and rotate along its length.

Young et al. (p. 1549) validate a computational fluid dynamic model, using particle imaging velocimetry and smoke visualization of the flow around actual locusts, and use the model to investigate the effect of measured changes in wing shape during a stroke cycle. The complexity of insect wing venation directly affects the aerodynamics of flight via the intermediary of wing deformation.

Anyone for D?

The chemistry of amino acids comes in two chirally distinct flavors—so-called L- and D-enantiomers. By far the most commonly used form of amino acids in all kingdoms of life is the L-form. Now **Lam et al.** (p. 1552; see the Perspective by **Blanke**) present the unanticipated observation that diverse bacteria release large amounts of various D-amino acids into the environment in a population density-dependent fashion and that D-amino acids act as extracellular effectors that regulate the composition, structure, amount, and strength of peptidoglycan, the major stress-bearing component of the bacterial cell wall.

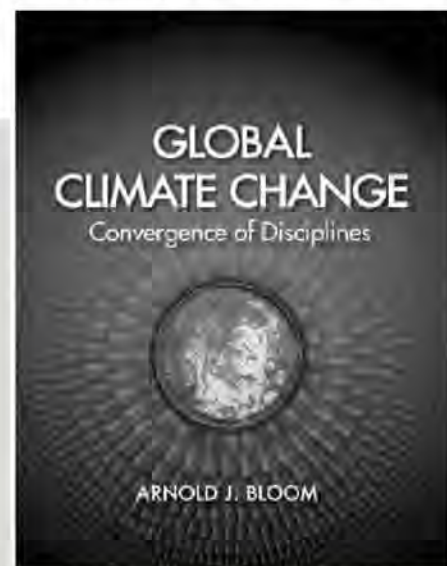
Desperately Seeking Glucose

Mutations in oncogenes and tumor suppressor genes allow cancer cells to outgrow their neighboring healthy cells. What microenvironmental conditions provide a selective growth advantage to these cells?

Yun et al. (p. 1555, published online 6 August) identify low glucose availability as a microenvironmental factor driving the acquisition of *KRAS* oncogenic mutations that allow cancer cells to survive and grow. In genetically matched colorectal cancer cells that differed only in the mutational status of the *KRAS* oncogene, mutant cells selectively overexpressed glucose transporter-1 and exhibited enhanced glucose uptake and glycolysis. When cells with wild-type *KRAS* were placed in a low-glucose environment, very few cells survived but most of the survivors expressed high levels of glucose transporter-1, and a small percentage of the survivors had acquired new *KRAS* mutations. Thus, glucose deprivation may help to drive the acquisition of cell growth-promoting oncogenic mutations during tumor development.

CREDIT: SUN ET AL.

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Biodiversity Policy Challenges

GLOBAL RESPONSES TO THE DETERIORATION OF BIODIVERSITY HAVE BEEN SLOW TO EMERGE, BUT next month the United Nations (UN) Environment Programme hosts a meeting* in Nairobi, Kenya, to discuss the next steps in establishing a new science/policy interface for biodiversity and ecosystem services. The response in this arena still lags far behind negotiations related to climate change, but the meeting is a chance to boost international action, based on strong scientific evidence. An important motivation for creating this interface is meeting the goals of international multilateral agreements, including the Convention on Biological Diversity (CBD), the UN Convention to Combat Desertification, and the Ramsar Convention on Wetlands. Unlike the UN Framework Convention on Climate Change, which has the Intergovernmental Panel on Climate Change, these environmental conventions lack a pre-convention science assessment and have no provision for subsequent government-endorsed, independent science. The meeting in Nairobi will debate, among other issues, how best to make up for this crucial omission.

Why is a robust biodiversity science/policy interface so important? The human population continues to mine the natural capital of Earth to support its growth, but the impact of this loss on human well-being is not widely understood in either public or policy spheres. Biodiversity is the building block of ecosystems that capture carbon and energy and cycle water and nutrients from the soil. These processes, and the structure of ecosystems that control them, benefit society with food, fuel, clean water, and climate regulation—so-called ecosystem services. The Millennium Ecosystem Assessment (MA), supported by UN agencies and nongovernmental organizations, concluded in 2005 that 60% of ecosystem services worldwide have become degraded, mostly in the past 50 years, primarily because of land- and ocean-use practices.

We lack information on global and local trends in most biodiversity components at the level of genes, species, and ecosystems, as well as baselines and standards for their assessment. We will certainly miss the CBD's target for reducing the rate of biodiversity loss by 2010 and also miss the 2015 environmental targets within the UN Millennium Development Goals to improve health and livelihoods for the world's poorest and most vulnerable people. Changes in ecosystems and losses of biodiversity have continued to accelerate. Even the most conservative estimates suggest that an area of tropical rainforest greater than the size of California has been destroyed since 1992, mostly for food and fuel. Species extinction rates are at least 100 times those in pre-human times and are expected to increase.

The situation is not hopeless. The MA outlined policy and management interventions at local to global scales that can reverse these trends, such as incentives for conservation based on payment for ecosystem services. Promising approaches to integrated land and sea use that will deliver multiple benefits require further scientific research. The challenges are complicated by continuing changes in climate, land use, human demography, and development, but the relevant science can be coordinated through international programs such as DIVERSITAS and the Earth System Science Partnership, and through international organizations such as the International Union for the Conservation of Nature. What is lacking is an effective dialogue between science-based information and relevant policy mechanisms to ramp up the speed and clarity of information flow.

We urge that scientists not only continue to generate the science that underlies good policies and decisions, but also become informed on policy issues that relate to their expertise and are highlighted in published research. In each nation, scientists need to take the crucial step of ensuring that research information reaches the relevant decision-making levels of government. In October, the 100 or so participating countries should bring not only their best policy negotiators but also their best scientists to the Nairobi conference. A commitment to an intergovernmental science/policy platform on biodiversity and ecosystem services is possible only if scientists take a serious step forward and become centrally involved.

— Harold Mooney and Georgina Mace

10.1126/science.1180935

*<http://ipbes.net/en/2ndMeeting/index.asp>



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BIOPHYSICS

The Mode Less Traveled By

One popular theme pervading recent chatter about enzyme catalysis is the linking of intrinsic macromolecular dynamics to function. The abundance of high-resolution protein structures has facilitated these studies, and Lezon *et al.* show just how much can be done even when only moderate-resolution structure models are available.

The nuclear pore complex (NPC) spans the nuclear envelope and supports passive transport between the cytoplasm and the inside of the nucleus. Modeling the NPC as a simple torus (86 nm in diameter, with a central hole 34 nm in diameter) revealed two low-frequency motions; these have the lowest energy and hence are the most populated. The first involved bending above and below the toroidal plane, whereas the second was an in-plane stretching and contraction of the torus into an ellipse. Refining the model by incorporating specifics, such as the eight spokes pointing inward from the toroidal rim and the greater mass on the cytoplasmic face of the NPC, did not change which two modes dominated. Some parts of the torus exhibited greater mobility (red) and some less (blue), and the eight-fold symmetry enhanced cooperative motions across the NPC. Finally, a comparison of these findings to the snapshots of *Dictyostelium* NPCs taken by cryoelectron tomography suggests that the bending mode underlies the reorganization of spokes observed during nuclear transport. — GJC

PLoS Comp. Biol. 5, e1000496 (2009).

MOLECULAR BIOLOGY

Local Connections Matter

Noncoding (nc)RNAs participate in many cellular processes; they are often associated with the regulation of gene expression, and most specifically with gene silencing—for example, XIST RNA in X-chromosome inactivation and AIR RNA in imprinted gene expression. Telomeres are protein–nucleic acid structures that cap and protect the ends of linear eukaryotic chromosomes. Recently, a noncoding, telomere-repeat–encoded RNA (TERRA) has been found to be transcribed from telomeric DNA.

Deng *et al.* show that knocking down the levels of TERRA results in a series of telomere defects. TERRA was found to associate with the proteins TRF1 and TRF2, which are components of shelterin, a complex that binds to telomeres. The interaction with TRF2—which localizes TERRA to telomeres—occurs through a domain of the protein that also binds to and localizes the origin recognition complex protein 1 (ORC1) to telomeres. ORC1 is suggested to be part of the telomere maintenance machinery, and TERRA facilitates the interaction between TRF2 and ORC1. Depleting TERRA resulted in both the loss of ORC1 from telomeres and a reduction in heterochromatin at chromosome ends. Furthermore, TERRA is capable of interacting with heterochromatin protein 1, indicating that, as for other ncRNAs, TERRA is involved in promoting heterochromatin formation specifically at telomeres, and that its various interactions contribute to chromosome integrity. — GR

Mol. Cell 35, 403 (2009).

ECOLOGY

Not in My Backyard

It is generally thought that anthropogenic noise is a contributing factor to declining nesting success for urban birds, but it appears that in some locales noise can have indirect and positive effects on some bird species. In woodlands adjacent to natural gas wells situated in the state of New Mexico, Francis *et al.* found that noise decreased the extent to which western scrub jays (*Aphelocoma californica*) preyed upon the nests of other birds. The relative intolerance of this predator for noisy habitats may result from the acoustic masking of their vocalizations by the compressors used in gas extraction. Although there was a general decline in nesting success and a reduction in species richness in response to noise, the escape from predation appeared to benefit species such as black-chinned hummingbirds and house finches, whose higher-frequency vocalizations are less vulnerable to interference from the sounds of human activities. — AMS



Curr. Biol. 19, 1415 (2009).

GEOCHEMISTRY

Included Clues

When natural diamonds form deep within Earth's interior, they often acquire small inclusions of other minerals that can change physical properties such as hardness and color. Although impurities tend to decrease a gem's aesthetic and economic value, mineral inclusions can provide valuable clues to how and where their more glamorous hosts were formed. Using high-resolution transmission electron microscopy and spectroscopy,

Continued on page 1477

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imagination at work

Continued from page 1475

Wirth *et al.* identified assemblages of mineral inclusions, including several carbonate and high-pressure silicate phases, in ~1-carat diamonds from central Brazil. Because some inclusions are only stable across a narrow range of temperatures and pressures, the diamonds can be traced as far down as the upper mantle, and possibly much deeper. Volatile-rich inclusions, such as PbCl_2 nanoparticles and KCl, suggest that salty hydrothermal fluids played an important role during formation. The isotopic signature of the host indicates that the carbon in these diamonds may have been derived from sedimentary organic material that was first deposited in the ocean—hence the salty inclusions—and then subsequently pushed several hundred kilometers below the surface at an ancient subduction zone. — NW

Earth Planet. Sci. Lett. 10.1016/j.epsl.2009.06.043 (2009).

IMMUNOLOGY

Long-Distance Commuting

B cell-mediated immunity is compromised in HIV-infected individuals even though these cells are not infected by the virus. How does HIV do this? One clue comes from the recent observa-



A Nef-containing conduit linking macrophages.

tions that B cells can express the viral protein Nef and that these Nef-expressing B cells exhibit impaired immunoglobulin class switching, a process whereby B cells expand their immunoglobulin repertoires to include additional classes and thus

enhance the response to pathogens. How Nef ends up in B cells, however, has been puzzling.

Xu *et al.* report that this occurs via long-range intercellular conduits formed between HIV-infected macrophages and B cells. Nef expression in macrophages drove conduit formation via an actin- and guanine nuclear exchange factor-dependent pathway. Nef then entered B cells via these conduits and once present in B cells, inhibited class switching. The authors then established the in vivo relevance of these findings by demonstrating that long-term nonprogressors (patients who have not developed AIDS) infected with Nef-deficient HIV showed evidence of normal class switching, whereas class switching was aberrant in patients harboring wild-type HIV. — KLM

Nat. Immunol. 10, 1008 (2009).

PHYSICS

Guiding a Rupture

Chemical transformations often involve two coupled stages of motion—electronic rearrangements within fractions of a trillionth of a second, followed by nuclear motion on a time scale one or more orders of magnitude longer. Over the past several decades, advances in laser technology have introduced pulses compressed sufficiently in time to glimpse these ultrafast dynamics, and in some cases to manipulate nuclear vibrational motion. A more recent goal is to achieve active control over electronic motion, by shaping even shorter pulses to map out the potential energy landscape and select particular pathways for the electrons to follow. The development of attosecond optics, using strong-field laser pulses of just a few optical cycles, with a controlled phase relationship between pulses, opens up the ability to pursue such designer reaction pathways. Experiments to date, however, have tended to probe the dynamics of rather simple, single-electron systems. Now, Znakovskaya *et al.* extend the principle of steering electrons with attosecond pulses to a more complex, multielectron system. They show that they can control the direction and energy of C^+ and O^+ fragments during the dissociative ionization of carbon monoxide molecules. Accompanying theoretical calculations explore the interplay of electronic excitations underlying the observations. — ISO

Phys. Rev. Lett. 103, 103002 (2009).

ASTRONOMY

A Pulsing Trio

Pulsars are rapidly rotating neutron stars that emit beams of electromagnetic radiation like distant lighthouses. It is estimated that 100 to 1000 pulsars orbit the galactic center with periods of less than 100 years, but only a very small fraction of these can be detected with current telescopes. Searching for the pulsars is important because they can inform us about the environment at the galactic center. Analysis of pulse arrival times can be used to derive the properties of the space-time and interstellar plasma there, and the number and ages of the pulsars can tell us about this region's past star formation history. Until recently, only two pulsars were known within 1° of the center of our galaxy. Now Deneva *et al.*, using data obtained with the Green Bank Telescope, a 100-m radio telescope, report the detection of another three pulsars. The observed properties imply that the trio is part of a population of pulsars associated with the galactic center. Monte Carlo simulations indicate that this population could be more numerous than previously estimated. — MJC

Astrophys. J. 702, L177 (2009).



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* Takahashi *et al. Cell*, 131, 861-872 (2007)

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INTEGRATING MEDICINE AND SCIENCE

Close-Up on the Bug



This new picture of the Bug Nebula (right), some 4000 light-years away, shows what the refurbished Hubble Space Telescope's new Wide Field Camera 3 can do. The instrument is 10 to 30 times more sensitive than the earlier camera, which snapped a picture of the same nebula—in far less telling detail (left)—in 2004. This image, taken on 27 July and released by NASA last week, will enable astronomers to get a richer understanding of the elemental composition of the butterfly-shaped object's gossamer wings, which span 2 light-years. Visit apod.nasa.gov/apod/image/0405/heic0407a_hst_full.jpg

A Termite's Perspective

Termites have a reputation as building-destroyers, but it was their building expertise that was on display this month at London's Southbank Centre. A human-scale replica of the central chimney of an African termite mound formed the centerpiece of a 3-day "Festival" celebrating the art and science of insects.

The termite pavilion was based on the first 3D scans of termite mounds, conducted by scientists in Namibia. Its builders hope to learn the secrets of the construction, which produces self-ventilating mounds that use the wind to keep the inner chambers at just the right temperature and humidity. The pavilion and other attractions drew more than 200,000 visitors, says Festival founder, naturalist, and writer Bridget Nicholls. More than 200 scientists, artists, and volunteers (wearing black-and-yellow bibs with "worker" on the back) came together to celebrate "how insects shape our world and how humans shape



Inside termite pavilion.

the world of insects." This was the world's second Festival; the first was held in 2006.

Darwin and Dance

Birds are noteworthy not only for their wit, charm, and sartorial splendor but also for their great dancing. So, for its contribution to this year's Darwin celebrations, London's Rambert Dance Company is putting on a bird-inspired show.

The company has the ideal scientific adviser: Nicola Clayton, an expert on the cognitive talents of jays and crows at the University of Cambridge (*Science*, 23 February 2007, p. 1074) and a lifelong dancer. Clayton helped the company's artistic director, Mark Baldwin, come up with a program that she calls a "distillation of Darwinian ideas about evolution, particularly sexual selection." One dance, for instance, is inspired by the elaborate displays of the six-plumed bird of paradise. In the wild, males inflate "a tutu" of feathers, then vigorously shake their heads and necks while sliding across a stage—all while being critically observed by a gallery of females. "The males are so constrained in their movements by female choice that it's comical," says

Clayton. Other dances in the program evoke blue manakins and bee hummingbirds.

The show, titled *The Comedy of Change*, runs 16–19 September at the Theatre Royal in Plymouth and 3–7 November at Sadler's Wells in London.



Nicola and Mark do the tango.

Putting Nobelists to Work

Two Nobel laureates who are stepping down from high-level positions aren't riding off into the sunset. Leland Hartwell, 69, who will retire next June as president of the Fred Hutchinson Cancer Research Center in Seattle, Washington, is heading south to lead the new Center for Sustainable Health at Arizona State University's Biodesign Institute. Hartwell, who won the Nobel for physiology or medicine in 2001 for uncovering the genetics of cell division, will oversee the development of biomarkers for predicting disease and yardsticks for measuring health outcomes. Meanwhile, 1989 chemistry Nobel laureate Thomas Cech, 61, completed a 10-year stint last spring as president of the Howard Hughes Medical Institute. Not content to confine himself to his telomerase research lab, he's also heading a biotechnology initiative at the University of Colorado, Boulder. A new building will bring together almost 600 researchers and support staff to tackle projects such as tissue engineering and virus imaging.



PNAS pulls
paper over
data ownership

1486



Science reform
starts with AP
courses

1488



SWINE FLU OUTBREAK

China First to Vaccinate Against Novel H1N1 Virus

BEIJING—No country has taken stricter measures than China to protect residents from pandemic swine flu. Although its draconian quarantine system sparked scientific debate and more than a few diplomatic spats before it was scaled back a couple of months ago, China's latest exploit is winning praise: Earlier this week, China was first off the blocks to launch a mass vaccination campaign against the novel H1N1 virus. "It's an impressive achievement," says biostatistician Ira Longini of the University of Washington, Seattle.

As the swine flu pandemic picks up steam, China is racing to immunize a sizable percentage of its 1.3 billion people before the pandemic's expected peak here this autumn or early winter. Epidemiologists here forecast that, without mass vaccination, tens of millions will become infected in China and hundreds of thousands will seek treatment, says Yang Weizhong, deputy director of the Chinese Center for Disease Control and Prevention (CDC).

China's lightning-fast vaccine effort might soften the blow. As of 14 September, Chinese authorities had 650,000 vaccine doses on hand and expect nearly 7 million more by the end of September. (U.S. manufacturers are slated to deliver 50 million doses by 15 October and 18 million a week thereafter.) In interviews with *Science*, the architects of China's campaign described how they managed to hold H1N1 at bay long enough to develop and test a

vaccine that they hope will avert a collapse of China's fragile health care system. "Our hope is to delay the peak and particularly to reduce severe cases and prevent deaths," says Chen Zhu, China's health minister.

China's aggressive campaign, crafted shortly after the world learned of the swine flu outbreak in Mexico last April, "was based on our particular situation: a huge population, poor health care in rural areas, and a limited stock of antiviral medicines," says Liang Wannian, the health ministry's deputy director general and chief of its Center for Public Health Emergencies. His team knew that China's health system would be overwhelmed if tens of thousands of people at any one time—including medical workers—were hospitalized with the pandemic H1N1 virus. Another concern was that China is a reservoir of H5N1 avian influenza, which kills roughly half the people it infects. "We wanted to reduce the opportunities for H1N1 and H5N1 to mix," says Liang.

The country's stringent measures to keep out the virus—early on, screening overseas passengers before they disembarked and quarantining all cases and contacts—appear to have worked, for a while: China reported its first non-imported case of pandemic H1N1 on 29 May, 2 weeks before the World Health Organization (WHO) raised the global pandemic alert to phase 6. But in early July, when it was clear the

Bamboo curtain. After striving to keep pandemic H1N1 out, China is now turning to mass vaccination.

virus could not be stopped, China "adjusted its strategy to the situation," says Liang, bringing it in line with most other countries.

By mid-August, nonimported infections in China were climbing, and in the past 3 weeks, their number has doubled to nearly 7000 confirmed cases, with three severe cases and no deaths. The early quarantine "bought us time," says Liang—enough time, that is, to make a vaccine.

China received H1N1 virus stock from WHO in early June, a little later than multinationals such as GlaxoSmithKline and Aventis Pasteur, says Liang. "Immediately, our industry put all their capacity into production," he says. Ten Chinese companies got to work, with the State Food and Drug Administration (SFDA) riding herd. The "green channel" SFDA created to speed review of vaccine development saved about a month, says Liang. Rather than wait for WHO to work up reference reagent for H1N1 vaccine hemagglutinin antigen (HA), the National Institute for the Control of Pharmaceuticals and Biological Products in Beijing, drawing on its experience with H5N1, developed a temporary reference. "If [the Chinese lab] was wrong, it would have been a waste of time," says Yang. When WHO released its standard reagent in early August, "ours matched almost exactly," Yang says. That saved another month.

On 21 July, Chen was the first person in China—perhaps in the world—to receive a novel H1N1 vaccine. The next day, China launched a clinical trial of three kinds of vaccine in 13,000 children and adults, testing preparations from all 10 companies as "a kind of internal control," says Liang Xiaofeng, director of the Chinese CDC's National Immunization Program. On 21 August, the health ministry announced that a single dose of inactivated split virus vaccine containing 15 micrograms of HA generated a robust antibody response in all age groups; a stronger effect was seen in adolescents and adults than in children under 12 and adults over 60.

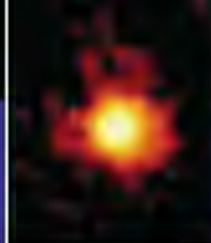
Chinese flu experts are still debating "whether one shot is enough or not," says Liang Xiaofeng. Preliminary results from two Chinese vaccinemakers—Sinovac and Hualan—indicate that a second dose, delivered 3 or 4 weeks after the first, offers "very limited

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The animal
sterilization
challenge

1490



Racing to gauge a
gamma ray burst

1494

further improvement," but analysis is continuing, he says. A single 15-microgram dose of a similar vaccine made by CSL Biotherapies in Parkville, Australia, elicited ample antibody levels in 116 of 120 adults, CSL epidemiologist Michael Greenberg and colleagues reported last week in *The New England Journal of Medicine*. "It's hard to imagine what additional protection would be afforded by a second dose," says Greenberg. He cautions that his group's study was limited to adults, so "it remains to be seen what is needed for children," who for their first seasonal flu vaccination require two doses.

In mid-August, says Chen, a cross-agency panel advised the central government that with schools about to reopen, a large-scale outbreak was inevitable. On 7 September, the State Council ordered Chinese companies to produce at least 65 million vaccine doses by the end of 2009, Liang Wannian says.

Earlier this week, China began vaccinating

doctors, nurses, border staff, and the roughly 200,000 soldiers and performers who will take part in celebrations at Tiananmen Square on 1 October to mark the 60th anniversary of modern China's founding. In the coming days, the campaign will begin in primary and secondary schools. Liang Wannian acknowledges that China can vaccinate only a fraction of its roughly 200 million school-age children. "But if you can get 30% of the population," he says, "the severe epidemic will be greatly mitigated." Longini disagrees. To tamp down pandemic H1N1 into something resembling mild seasonal flu is likely to require about 70% vaccine coverage, he and colleagues predicted in a paper published online last week in *Science*.

Vulnerable groups—pregnant women and individuals with chronic respiratory illness or cardiovascular disease, for example—will also have priority, although Liang Wannian worries that in China "pregnant women are not very

keen to accept the vaccine." He says China is "closely observing" a vaccine trial in pregnant women launched last week in the United States.

Thanks to a greatly enhanced flu-surveillance network, China plans to first focus its vaccination campaign on harder-hit regions: Shanghai and the Pearl River delta of southern China, which has three teeming cities—Guangzhou, Hong Kong, and Macau—in close proximity. In the delta and in Shanghai, China's business hub and a major port of entry, more than 30% of influenza-like illnesses are caused by pandemic H1N1, compared with a few percent in other parts of China. (The percentage currently exceeds 90% in the United States.) Vaccinating first in the delta, Shanghai, and the capital, Beijing, "will build up a barrier of immunity among the population and reduce the risk to other regions," says Liang Wannian. If that barrier holds, Chen insists, "we can keep the situation under control." —RICHARD STONE

RESEARCH AWARDS

Laskers Honor Five Scientists and a Mayor



Honored. Yamanaka, Gurdon, Lydon, Sawyers, Druker, and Bloomberg are 2009 awardees.

Five biomedical researchers and the billionaire mayor of New York City have been selected for the 2009 Lasker Awards. Considered the most prestigious medical research awards in the United States, 76 past recipients have gone on to win a Nobel Prize.

John Gurdon of the University of Cambridge in the United Kingdom and Shinya Yamanaka of Kyoto University in Japan will receive the Albert Lasker Basic Medical Research Award for their work on nuclear reprogramming. The Lasker-DeBakey Clinical Medical Research Award goes to Brian Druker of Oregon Health and Science University in Portland; Nicholas Lydon of Granite Biopharma in San Diego, California; and Charles Sawyers of Memorial Sloan-Kettering

Cancer Center in New York City for the development of drugs to treat chronic myeloid leukemia (CML). The Mary Woodard Lasker Award for Public Service honors Mayor Michael Bloomberg for "employing sound science" in his campaigns to ban smoking and to combat obesity and for his philanthropic activities. Bloomberg, an independent who built a media empire, is seeking his third 4-year term in November.

Gurdon overturned the prevailing idea that specialized cells lose the genes necessary to become other cell types with his successful transplantation in the 1960s of nuclei from frog intestine and skin cells into frog egg cells, creating a viable animal. In 2006, Yamanaka took Gurdon's work to the next level by reprogram-

ming adult mouse skin cells into induced pluripotent stem cells (iPS). Yamanaka found a set of genes that, when inserted into a specialized cell's genome, caused the adult cells to revert back into stem cells.

The clinical award recognizes pioneers in the development of Gleevec, which took a different approach to treating CML by targeting the enzyme called BCR-ABL, which becomes dysfunctional in CML. Once facing a death sentence, CML patients can now expect a 90% survival rate. Their subsequent work has led to the development of another drug that attacks resistant forms of CML.

Each recipient will receive a \$250,000 prize at the foundation's 2 October ceremony in New York City.

—MICHAEL TORRICE

BIOTECHNOLOGY

Researcher, Two Universities Sued Over Validity of Prostate Cancer Test

A Johns Hopkins University (JHU) researcher whose reports of a potential new blood test for diagnosing prostate cancer generated excitement—but also skepticism—is now being sued by his industry sponsor for scientific fraud. The company, Onconome Inc., says it poured millions of dollars over 5 years into the laboratory of Robert Getzenberg and alleges that he presented the company with misleading data. The lawsuits say that the biomarker test, which Getzenberg claimed could distinguish between cancerous and normal tissue, was “essentially as reliable as flipping a coin.” Onconome in Redmond, Washington, is suing Getzenberg, JHU, and the University of Pittsburgh (Pitt), his previous institution, for unspecified damages.

Legal experts say it is not unusual for a company-academic partnership to end up in court, but rarely has such a lawsuit involved allegations of scientific fraud. Citing ongoing litigation, both Pitt and JHU declined to comment on the suits. Getzenberg’s attorney also declined to comment beyond a statement from JHU that “Dr. Getzenberg continues to be a faculty member in good standing and his research is continuing.”

In the cancer research community, meanwhile, news reports of the suit filed against Pitt in federal court on 2 September—and a similar state court suit originally filed against Pitt and JHU last February—have cast another shadow on the field of cancer biomarker research, which some say has a long history of hype but few successes.

The research at issue began when Getzenberg was a graduate student in the lab of JHU cancer biologist Donald Coffey. In the early 1990s, Coffey’s team reported that a certain protein from the nuclear matrix of prostate tumor cells is present in prostate cancer tissue but not in normal prostate tissue.

According to the Pitt complaint, in 2001 while at Pitt, Getzenberg told Onconome’s potential investors that nuclear proteins from prostate tumor cells could be detected in blood and offered an alternative to the prostate specific antigen test, which has well-known limitations. Onconome was founded in 2001 to develop antibody-based tests that detect one such protein, which Getzenberg discovered and called Early Prostate Cancer Antigen (EPCA). The company “depended entirely” on Getzenberg to

conduct its scientific research through research agreements with Pitt and later JHU, the suit says.

In more than 20 updates to Onconome’s board, the Pitt suit says, Getzenberg reported results for EPCA and biomarkers for other cancers that he described as “amazing”: sensitivities and specificities approaching 100%, which means that the tests identified nearly all cancerous samples and rarely resulted in false positives. Two top medical journals



Disputed claims. A company alleges that Robert Getzenberg misrepresented his lab’s data on cancer biomarkers.

rejected a paper by Getzenberg on a second biomarker called EPCA-2, the suit says. However, he published a paper on EPCA-2 in the April 2007 issue of *Urology*. It drew widespread media coverage, thanks to a press release from JHU, where Getzenberg had moved in 2005 to take over for Coffey as research director of the James Buchanan Brady Urological Institute.

When Onconome hired its own scientists to develop and market the EPCA tests, they were unable to replicate Getzenberg’s experiments. The Pitt suit says that when Onconome compared lab records that were

“only recently obtained,” it found that many statements from Getzenberg were “false.” The suit alleges that he exaggerated statistical associations, “cherry-picked the data” to report favorable results, that his technician broke the blind on samples, and that he falsely claimed to have determined the DNA sequence coding for EPCA. In the end, the suit claims, EPCA markers “were and are imaginary.”

The lawsuit filed in federal court in Pittsburgh and a similar amended complaint filed in circuit court in Baltimore City in July against JHU and Getzenberg include claims of fraud, breach of contract, and “failure to supervise.” Onconome, which says its losses exceed \$13 million, asks for damages to be determined at trial and attorney’s fees. In a motion to dismiss filed in April, JHU claims that Getzenberg’s research activities “were in conformity with the ... state of knowledge in the scientific field.”

Research integrity expert C. K. Gunsalus of the University of Illinois, Urbana-Champaign, wonders whether the universities are conducting a scientific misconduct investigation of Getzenberg, who also had federal funding for his biomarker studies. JHU declined to comment; Pitt said it is not investigating, noting that Getzenberg has been gone for several years.

Several cancer researchers informed *Science* that they regarded EPCA and other biomarkers from Getzenberg as promising but in need of more testing. Arul Chinnaiyan of the University of Michigan, Ann Arbor, says the sensitivities reported were “stunningly high,” but he notes that that can happen in small, preliminary studies. Others have been more dubious. In a 2007 critique published in *Clinical Biochemistry*, University of Toronto biochemist Eleftherios Diamandis questioned whether nuclear proteins from tumors would be present in blood in quantities that could be detected with Getzenberg’s assay.

The case is another black eye for cancer biomarker research. Last year, federal regulators told a company that had begun marketing an ovarian cancer test developed at Yale University to hold off because the test had not yet been properly validated. A few years earlier, doubts were raised about another test for ovarian cancer based on protein signatures. “For decades, the field has been littered with the bodies of groups that have made dramatic claims that didn’t pan out,” says epidemiologist David Ransohoff of the University of North Carolina, Chapel Hill, who has called for more rigorous studies before going to market.

—JOCELYN KAISER

CREDIT: JHM

MATERIALS SCIENCE

DuPont Scientist Accused of Stealing Company's Trade Secrets

A Chinese-born scientist, one of the leading researchers in the field of next-generation display technologies, has been fired by DuPont, which alleges he attempted to steal company secrets. The scientist, Hong Meng, now faces both a civil lawsuit from the company and a criminal investigation by the U.S. Department of Justice. If charged with criminal wrongdoing, Meng could face up to 10 years in jail and a \$5 million fine.

The case marks the second time in less than 4 years that DuPont has filed suit against a researcher with ties to China. In November 2006, Gary Min, a former researcher at the company, admitted to stealing company data valued by federal officials at \$400 million. Min pleaded guilty and was sentenced to 18 months in prison.

Meng, a permanent resident of the United States, earned his master's degree from Peking University in Beijing in 1995 and his Ph.D. from the University of California, Los Angeles (UCLA), in 2002. DuPont hired Meng in November 2002 to work on organic light-emitting diodes (OLEDs), a technology that recent industry reports suggest could swell to a \$7.1 billion market by 2016.

Meng worked at DuPont's central research facility in Wilmington, Delaware. But according to court documents filed in the Delaware Court of the Chancery on 21 August, he was preparing to transfer to work for the company in China. As part of a review for this transfer, company officials examined his computer hard drive and discovered an "illicit connection" to Peking University. According to the lawsuit, Meng had accepted a position at the university. And an investigation of his laptop and personal computer revealed that Meng had downloaded confidential company material. "It was also confirmed through a review of documents on the computer that Dr. Meng has engaged in a surreptitious relationship with Peking University over a long period of time, and that he plans to launch or already has launched a program with Peking University aimed at commercializing OLED technology for industrial applications in direct competition with DuPont," the lawsuit states.

Sizzling. The market for OLED displays is in the billions of dollars and rising fast.

"Hong Meng's employment with the company was terminated and we promptly filed suit to ensure that he not use or disclose DuPont trade secrets," said Thomas L. Sager, DuPont's senior vice president and general counsel, in a written statement. Meng could not be reached for comment. His lawyer, Joseph Bernstein of Bonita Springs, Florida, said that Meng is cooperating with the Justice Department investigation. "It's an unfortunate situation for everyone involved," Bernstein says.

Fred Wudl, a chemist at the University of California, Santa Barbara, and Meng's Ph.D. adviser at UCLA, says that Meng was one of the best students he's ever had. "He's a very inventive guy," Wudl says. "He was very straight arrow in the group."

Another friend and chemistry colleague of Meng's who asked not to be identified says that Meng is being "mistreated" and that the case arose from a misunderstanding. Meng's colleague says that at DuPont, Meng invented improved OLED materials that shine blue light and was working to patent them for the company. The company files Meng downloaded were simply to help in filing the patents. As for the "illicit" relationship with Peking University, Meng's colleague says that Meng was looking into accepting a position with the university and had written a standard and somewhat boilerplate proposal listing areas his group would work on. Meng's colleague adds that Meng was aware that his employee agreement with DuPont meant he was not allowed to develop competing technology. "He had no intention to do so."

—ROBERT F. SERVICE



ScienceInsider

From the Science Policy Blog



The investigation into the death last week of Annie Le, a **24-year-old Yale University pharmacology graduate student**, has led authorities to temporarily close the building in which she worked, which houses the Yale Stem Cell Center as well as interdisciplinary programs on immunology and vascular biology. "All research in the Amistad Building is at a standstill—even people who need reagents for an ongoing clinical trial are unable to have access," stem cell researcher Diane Krause said on Monday. In other bad news from Yale, university President Richard Levin announced that the school expects a **\$150 million deficit each year for the next 4 years**, which will slow recruitment for science positions.

The Environmental Protection Agency, Department of Agriculture, and other U.S. agencies have announced plans to devise **new controls on agricultural runoff, air pollution, and sewage to protect the Chesapeake Bay**. A new report highlights the need to focus on adaptive and ecosystem-based management. "This will require significant revision of the existing Chesapeake Bay Program goals and structure," the report said. "The desired outcome is to transform the partnership to dramatically increase the involvement of citizens and local governments, and better align federal, state, NGOs, and academic efforts."

A U.S. federal judge denied a request by environmentalists and animal-welfare groups to stop the hunts of the **Northern Rocky Mountain gray wolf** in Idaho and Montana. U.S. District Judge Donald Molloy ruled in Missoula, Montana, that the plans to kill more than 20% of the estimated 1350 wolves in the two states would not cause long-term harm to the species.

Molloy also said in his 14-page ruling that the federal government violated the Endangered Species Act in May when it lifted protections for the wolves in Idaho and Montana but not animals in Wyoming. He called the move "a practical determination that does not seem to be scientifically based."

For more science policy news, visit blogs.sciencemag.org/scienceinsider.

SCIENTIFIC PUBLISHING

Paper Retracted Following Genome Data Breach

Here's a nightmare scenario: You go to the Web site of a leading journal, and there on your screen is a paper based on data you have painstakingly gathered but not yet had time to analyze.

That's what happened to psychiatrist Laura Bierut, who discovered last week that other researchers had broken an embargo on use of data she and her colleagues had deposited in dbGaP, the National Institutes of Health's (NIH's) database of genotypes and phenotypes. Bierut, a professor at Washington University in St. Louis in Missouri, and colleagues had collected the data as part of genetic studies of alcoholism and other addictions collectively known as SAGE (Study of Addiction: Genetics and Environment).

dbGaP was established in 2006 to facilitate sharing of the oceans of genetic data generated by federal grantees. Other scientists can submit papers based on the material



Scooped. Another team broke the database embargo and published a paper using Laura Bierut's data.

after an embargo period of 9 to 12 months so those who generated the data can have first crack at analyzing them.

The SAGE embargo ends on 23 September. But on 31 August, a paper based on SAGE data appeared online in the *Proceedings of the National Academy of Sciences* (PNAS). In it, a team led by Heping Zhang, a biostatistician at Yale School of Public Health, reported a positive association between a gene called *PKNOX2* and addictions in women of European origin. It was submitted to the journal last March, breaching the embargo by 6 months.

Bierut immediately shot off e-mails to Yale, Princeton University (home of co-author and National Academy of Sciences member Burton Singer, who contributed the paper), PNAS, various NIH officials, and colleagues. "[T]his was likely an unintentional act, [but] this incident remains very concerning," she wrote, adding that it "sends

SCIENTIFIC PUBLISHING

PNAS Nixes Special Privileges for (Most) Papers

The *Proceedings of the National Academy of Sciences* will discontinue an option for submitting papers that often put prestigious scientists in an awkward fix with colleagues and, at its worst, editors admit, allowed some scientists to subvert peer review and shoehorn dubious papers into print.

As a house organ, the journal has always had an idiosyncratic submissions process. National Academy members, as elite scientists, could shepherd their own work through peer review with less vetting than at other publications by "contributing" a paper. They could also "communicate" a paper on behalf of colleagues who had not been elected to the academy's august ranks. In 1995, PNAS began allowing nonmembers to submit directly to the journal without endorsement, but it grandfathered in the two older submission routes.

In practice, "communicating" a colleague's paper meant that a member lined up referees to review it before PNAS ever saw it. This increased the chance of a favorable reception—and looked suspiciously like cronyism to outsiders. Partly because of that perception, PNAS announced last week that it will end the "communicated by" option

(known as Track I) as of 1 July 2010. The move will not affect the privileges of academy members to line up reviews before they submit their own papers to PNAS, however.

The editorial board of PNAS had been discussing the move for years. "It was clear we needed to do something," says David Chandler, a chemist at the University of California, Berkeley, and an associate editor of PNAS. "We often had members submitting when they were not experts on the topic, or sometimes the referee reports were cherry-picked." The majority of academy members supported the move, he notes. When polled by the board this summer, 80% voted to end the submission route.

Nevertheless, many members had nagging reservations. Even Chandler argued for reforming rather than killing Track I. "I always thought academy members should have a chance to promote work that was not finding its way into established journals because it was so unorthodox."

Other academy members were nostalgic. "My ambivalence was very simple," said Brian Hoffman, a chemist at Northwestern University in Evanston, Illinois.

"Once upon a time, members went out of their way to assist me, so I feel the obligation to do the same now."

Still, Hoffman admits the new policy will spare him some awkward obligations. Members could communicate just two papers per year, so colleagues scrambled to get his attention. And it was hard to turn them down without insulting them, he says. "If you feel it's the wrong thing to do, it's hard to look your colleague in the eyes and say no."

Robert A. Weinberg, a biologist at the Whitehead Institute in Cambridge, Massachusetts, agrees: "One felt obliged out of friendship to communicate things." What's more, says Weinberg, too often publication "depended on whom one knew, and who had good connections."

An example of alleged gamesmanship popped up online 28 August in PNAS. Lynn Margulis, the noted biologist at the University of Massachusetts, Amherst, communicated a paper by Donald Williamson, a retired marine biologist in the United Kingdom. In it, Williamson promoted his long-held, intriguing—and, say most other biologists, almost certainly misguided—theory

CREDIT: JOE ANGELES/WUSTL MAGAZINE

a very chilling message to investigators.”

The responses were swift. Yale took down a press release it had posted about the study. NIH froze the researchers' access to dbGaP. And on 9 September, *PNAS* retracted the paper (www.pnas.org/content/early/2009/09/09/0910252106.full.pdf).

What went wrong? That's still not clear. When an investigator gets permission to access the raw data stored at dbGaP, he or she signs an agreement pledging not to submit any paper before the embargo date. Author Zhang, who signed the access agreement last year, told *Science* he doesn't want to say anything until NIH concludes its review.

Alan Guttmacher, acting director of the National Human Genome Research Institute, and Elizabeth Nabel, director of the National Heart, Lung, and Blood Institute, said in an e-mail that the NHGRI Data Access Committee is working with all parties to figure out how the breach occurred—and how to ensure it won't happen again. But, they wrote, “We do not anticipate that the underlying ... publication

policy will change based on a single, unfortunate incident.”

Bierut agrees with NIH that data sharing is a good thing, and the policy should stay in place. “I think NIH and *PNAS* moved very quickly to resolve the issues,” she says. “The good news is I think the system worked.”

The paper is still on the *PNAS* Web site. *PNAS* Editor-in-Chief Randy Schekman says, “We thought about whether it was feasible to remove the online version and decided against it,” because of the “very awkward consequences—librarians get confused about papers being cited that no longer exist.” Schekman says there is not much likelihood that the paper will be accepted if it's resubmitted after the embargo date. Instead, “we've invited Laura Bierut to submit.” Schekman says *PNAS* will probably expand

its author checklist to include a question about whether any data used is under embargo. He adds that “Dr. Zhang may be further sanctioned” by *PNAS* if the circumstances warrant such action.

The episode still leaves a bad taste in some mouths. Michael Miller, a psychologist at the University of California, Santa Barbara, says it has reinforced sentiments of those who feel NIH's policy of gene data sharing is too generous. “Other teams can start working with the data almost as soon as the group that collected the data,” he points out. “They can write a dozen papers ahead of time and submit them all on that 1-year embargo date.” Nicholas Martin, a behavioral geneticist at the Queensland Institute for Medical Research in Brisbane, Australia, agrees. The relatively short embargo periods “leave ... the gate open for predators with no investment in the data to do quick-and-dirty analyses that pick the eyes out of the data without looking at any of the subtleties,” he says. “This breach only heightens these concerns.”

—CONSTANCE HOLDEN

about the origins of caterpillars and butterflies. Current biological theory argues that they were always a single species and that each stage evolved via natural selection. Williamson argues instead that two distinct species (one caterpillar-like, one butterfly-like) somehow fused into a hybrid way back when. One species' sperm must have fertilized the other's eggs, transferring genes laterally across species in a non-Mendelian fashion.

Margulis was unavailable for comment, but Williamson says, “Lynn Margulis is prepared to put her name and reputation on the line” to prove that “genome mergers” occur in evolution, a position his paper supports. He also says he knows that Margulis sent his paper to a half-dozen academy reviewers. Williamson says that he thinks they were all positive reviews, but Margulis told *Scientific American* last week that she canvassed six or seven reviewers to find the two positive reviews necessary to push the paper through.

Randy Schekman, a biologist at Berkeley and the editor-in-chief of *PNAS*, says, “I've



Wrong track. *PNAS'* Track I produces many highly cited papers, but Editor-in-Chief Randy Schekman concedes that members sometimes abuse it.

spent a lot of time fielding angry e-mails questioning how this got through.” In general, he says, “we from time to time have members who have an agenda and can usher a paper through against very strong opposition.” As with all communicated and contributed papers, a member of the editorial

board did review and approve Williamson's paper; *PNAS* is now investigating the publication process, Schekman said.

Such scenes might seem an inevitable result of scientists lining up their own referees. But *PNAS* will not take the ultimate step of curbing such privileges for members. Schekman said the rejection rate for communicated or contributed papers that reach *PNAS* is a few percent, whereas the rejection rate for standard submissions is 80%. In 2008, the journal published 4000 papers, of which about 600 were communicated and about 750 contributed.

Schekman defends member contributions by noting that many are among the journal's most highly cited papers.

He also says the contribution option keeps academy members active in *PNAS*. “It's an unusual and interesting feature to distinguish the journal. And if we didn't have this, I worry members wouldn't be quite as helpful as they are.”

—SAM KEAN

U.S. SCIENCE EDUCATION

Revisions to AP Courses Expected to Have Domino Effect

Last month, Jeffrey Lamb began teaching Advanced Placement (AP) chemistry for the first time at Woodmont International Baccalaureate High School in Piedmont, South Carolina. The public school's decision to offer the course reflects the explosive growth of the AP program, a suite of 38 courses intended to mirror an introductory college course.

Last year, 442,000 students—up from 66,000 in 1989—took one of the six AP science offerings (in addition to chemistry, there are three physics courses and one each in biology and environmental science) as school districts around the country increasingly use them as a marker for a quality education. But that growth has unwittingly compounded what a slew of reports have found to be a flawed approach to teaching science: too much emphasis on facts and memorization and too little attention to the underlying concepts and how science is actually practiced.

Because students can receive college credit if they pass the AP exam in a particular subject, colleges have insisted that the AP course include everything covered in those introductory courses. The result has been a pedagogical nightmare. “AP teachers have had to resort to memorization and factual recall as a way to cover everything that could be on the exam, although that was never our intention,” admits Trevor Packer of the College Board, the New York City-based nonprofit association that operates the program.

But that is changing. In July, the College Board unveiled the first piece of a major revision of the AP syllabi for science. The new courses will emphasize conceptual knowledge, updated regularly and learned by doing, along with teaching how scientists ask and answer important questions. And this week, the board released a related document, called *Standards for College Success*, that suggests how science should be taught throughout secondary (middle and high) school (professionals.collegeboard.com/k-12/standards).

Lamb doesn't need convincing. Instead of drilling students on how to apply a particular algorithm, he says, “I'd much rather

that students are able to explain the underlying concept to me, in English, and show me they understand something about how nature builds the stuff around us.” Lamb spent the summer whittling down the massive AP chemistry syllabus to fit into a manageable 1-year course. As department chair, he also tweaked the school's other science courses so that students would be better prepared to handle the AP material.



Cellular detectives. Julie Zedalis helps her AP biology students apply their knowledge of cell types to identify “mystery” cells and aquatic organisms.

Biology is the first of the AP science courses being revised, and there's a consensus that it's also the course most in need of drastic changes. “We've learned so much since I began teaching in the 1980s, and it all gets added to the curriculum. But nothing gets dropped,” says Julie Zedalis of The Bishop's School in San Diego, California, a private school whose students historically lead the nation on the AP biology exam.

Zedalis co-chaired the board's most recent commission to revise AP biology. “Everybody has their favorite domain. But people are going to have to be willing to give up something for the good of the program,” she says. Robert Dennison, an award-winning AP biology teacher at Lee High School in Houston, Texas, and another member of the commission, says he heard “a big sigh of relief” from teachers after they read the commission's report and realized a slimmer curriculum would give them the opportunity “to share their passion for science.”

Restructuring the course will also require the College Board to revise its high-stakes final exam. “Students will need to be given options, the chance to demonstrate their knowledge through examples that draw on what topics they have covered,” says Dennison.

Zedalis thinks that won't be a problem if teachers understand that the goal is for students to understand a particular topic well enough to be able to apply those principles to novel situations. “If you're teaching osmosis and diffusion, you can talk about the movement of gases from the lungs to the capillaries, or the walls of the intestine, or how plants transport water,” she explains. “You don't need to do all of them.” The revised course, she adds, eliminates the need to teach “the organ of the day” in a mad dash to cover every human system.

The College Board hopes to announce in December a timetable for revising all the science courses. A tentative implementation date of 2012 for AP biology, says Packer, hinges on training enough teachers in the new course and preparing a new exam.

Although in theory the changes in the AP syllabi may eventually filter down to

AP BIOLOGY EXAM

Old

Which of the following physiological effects would likely occur first in a volunteer who was breathing air from which the CO_2 was removed?

- a) Decreased blood pH
- b) Decreased respiratory rate**
- c) Increased respiratory rate
- d) Increased pulse rate
- e) Increased blood pressure

New



The equation above shows a reversible reaction that occurs in blood. An Olympic marathoner training at high altitude in Colorado feels dizzy and begins hyperventilating while taking a run. Her blood pH is elevated, resulting in alkalosis. How will normal blood pH be restored?

- a) An increase in O_2 concentration in the plasma will lead to an decrease in H^+ concentration
- b) An increase in CO_2 concentration in the plasma will lead to an increase in H^+ concentration**
- c) A decrease in sweating will lead to an increase in HCO_3^- concentration
- d) A decrease in respiration will lead to an increase in plasma O_2 concentration

Manipulate, not memorize. To answer the top question, students must first have memorized the relevant equation. The new assessment provides the equation and asks student to use it in solving a real-life problem. (The answer to both questions is B.)

other science courses, the board hopes its new college-readiness standards will accelerate the process. The standards are aimed at preparing students for college-level work as well as for the various AP courses and track closely the AP revisions.

At the top are a handful of big ideas in each discipline; in the life sciences, for example, they include evolution, the storage and transmission of information, and the use of energy to carry out essential functions. That's followed by a series of core principles. One new wrinkle links content knowledge to the actual practice of science. The final layer is a set of performance expectations: what students should know, understand, and be able to do to demonstrate their mastery of the subject.

Although setting standards is the domain of each of the 50 states, the College Board's recommendations come at an opportune time. In June, the governors of 46 states embraced the idea of voluntary common standards for mathematics and language arts. Cheered on by Education Secretary Arne Duncan and industry leaders, the initiative (corestandards.org) hopes to come up with recommendations early

next year for state legislators and school officials, who will decide how—or whether—to incorporate them into their existing standards.

Science is not yet on the table, says Michael Cohen, president of Achieve Inc., a state- and industry-backed nonprofit group that is helping to draw up the math and language standards. College and career-readiness skills are easier to define in math and English than in science, he says, “and there’s no such thing as remedial science.” The initiative’s Web site notes, however, that it expects to tackle “a common core of standards in science” once work is completed on math and English. Cohen also says he would hope that “anybody working on science standards would look at what the College Board has done.”

Packer thinks school districts will start “right away” to align middle and high school courses to the revised AP syllabi because of their “huge appetite ... to help students perform at a higher level.” Lamb is less sanguine. “Realistically, I doubt that things are going to change significantly,” he says. “But I’d love to see that scenario. It’s what most teachers want to be able to do.”

—JEFFREY MERVIS

LOW-INCOME COUNTRIES

A Boost for Vaccine Development

Maurice Hilleman, a pioneering vaccine scientist who spent much of his career at Merck & Co., is credited with developing more vaccines than any other scientist. Although he died in 2005, his name could be associated with many more. This week, Merck and the U.K. biomedical charity Wellcome Trust established a nonprofit vaccine development institute and named it after Hilleman. The \$145 million private-public partnership will focus on creating vaccines for low-income countries, with an emphasis on making existing vaccines more affordable and easily distributed and on combating unmet disease needs, such as a vaccine for group A streptococci.

The planned MSD Wellcome Trust Hilleman Laboratories, which will be based in India, will seek to move existing ideas from “concept to proof of concept,” says Mark Feinberg, Merck’s vice president of medical affairs and policy. He notes that product development experience is a “rare commodity” outside the vaccine industry, and academic and government scientists typically struggle to translate discoveries into formulations suitable for clinical trials or even large-scale vaccine production. Biotech companies which normally can’t

afford to target low-income markets, might also collaborate with the institute while preserving product rights for richer countries.

The initial financial commitment from the two partners is for 7 years, although Ted Bianco, director of technology transfer for the Wellcome Trust, says the charity will consider additional funding if the institute is successful. The center may also earn revenue from licensing its advances for use in developed countries. Merck and Wellcome Trust representatives will have equal representation on the institute’s governing board, and the company will have first right to negotiate for the lab’s intellectual property.

The institute’s initial projects are still being discussed, but making heat-stable versions of known vaccines is a general goal. A vaccine for group A streptococcus is also a likely target, says Feinberg. In developed countries, rapid strep-throat assays and antibiotics have made developing a vaccine appear unprofitable. Yet the bacteria still kill more than 400,000 a year worldwide. Brian Greenwood of the London School of Hygiene and Tropical Medicine calls the new institute a “good idea,” as more needs to be done to “bridge people in the lab and big pharma.”

—JOHN TRAVIS

ScienceNOW.org

From Science’s Online Daily News Site

Forest a Desert, Cool the World

For more than a century, a few scientists have daydreamed of transforming much of the Sahara desert green, with a lush inland sea or vast tracts of farmland. Now researchers say they have actually found a way to make such a scheme work—and slow climate change in the process. <http://bit.ly/19DYKU>



A Mystery in the Desert

In the early 1970s, archaeologists unearthed an unusual find in an ancient Chilean cemetery: the skulls of four women whose faces had seemingly been eaten away. None of the other 500-to-1000-year-old bones in the cemetery displayed the same disfigurement. Now, thanks to the region’s arid climate, which helped mummify some of the women’s facial tissue and brains, scientists think they have figured out what happened. <http://bit.ly/1XFPAV>

Birth Control for Stars

Gravity sometimes needs a restraining hand. New findings show that the giant clouds of dust and gas that pervade the universe, out of which form all of the stars and other assorted celestial bodies, depend on magnetism to regulate their collapse. If confirmed, the study would resolve a long-standing mystery about the star-forming process. <http://bit.ly/32RZRR>

Brain Scans for Schizophrenia?

If you’re at risk for heart disease, doctors can monitor your cholesterol. But psychiatrists don’t have an analogous test for mental illnesses. That may change with a new discovery: Scientists have pinpointed a small spot in the brain where increased activity raises the likelihood that high-risk patients will develop schizophrenia. <http://bit.ly/UW89c>

Read the full postings, comments, and more on sciencenow.sciencemag.org.

A Cure for Euthanasia?

A nonsurgical sterilant could reduce the global population of homeless dogs and cats, but there hasn't been money to develop one—until now

NINETY KILOMETERS SOUTHWEST OF Montgomery and a few decades shy of the modern world lies Oak Hill, Alabama, the smallest town in one of the poorest counties in the state. There are 23 homes, one gas station (which doubles as a general store), and a post office staffed by a single employee.

Oak Hill doesn't have much—but it does have cats. Cats that congregate in barns and under sheds. Kittens born in long-vacant restaurants and antique shops. Pregnant queens abandoned in the woods. Tomcats that fight raccoons for food.

There are no animal-control services in Oak Hill, so the cats keep breeding. And dying. Cars mow them down on the state highway; locals shoot them on site; and those that do make it to overcrowded, far-away shelters are euthanized within days.

A few fortunate felines find their way to the back porch of David Fuller, a retired electronics engineer who, as a contractor for NASA, spent years ensuring that rocket components destined for space survived their environment. These days, Fuller and his wife do the same for Oak Hill's cats. They trap the ones they can and try to find homes for them. They bottle-feed kittens whose

eyes have been glued shut by dust. And they drive an hour each week to the nearest Wal-Mart, where they load their pickup truck with 8-kilogram bags of dry cat food.

Thirty-five feral cats call Fuller's property home, and he takes care of another 30 at his mother's farm in a nearby town. Despite Fuller's best intentions, however, he can't possibly keep up. He's running out of people to give the cats to, and the overflowing shelters will no longer take them. He's spayed and neutered a few, but he can no longer afford the \$100 surgeries. And so the cats keep breeding.

The problem isn't confined to Oak Hill. Humane organizations throughout the

United States can't surgically sterilize homeless cats and dogs fast enough to control their numbers, and developing countries with dangerous feral dog populations—such as China and India—fare even worse. As a result, millions of dogs and cats are euthanized in U.S. shelters each year, and millions more are shot and poisoned around the globe. "There's almost no hope of making any kind of dent in the problem with surgery," says Joyce Briggs, the president of the Portland, Oregon-based Alliance for Contraception in Cats and Dogs (ACC&D).

For the past decade, ACC&D and other humane organizations have pushed for a nonsurgical alternative to traditional spay/neuter surgery—something cheaper and faster, such as a vaccine or a pill. "Something," Briggs says, "that would let us reach far more animals with the same resources." Researchers have developed similar products for wildlife, but they have turned out to be ineffective or impractical for use in companion animals. Lack of funding and interest has slowed further progress.

That may be about to change, thanks to a U.S. billionaire named Gary Michelson, who has announced \$75 million in



Vagabonds. About 30 million feral cats roam the streets of the United States.

Death row. Overcrowded U.S. shelters euthanize nearly 4 million dogs and cats each year.

grants and prize money for the development of a single-use, nonsurgical sterilant for dogs and cats. Suddenly, researchers who had abandoned this work are ramping up their efforts again. And those who had never considered the problem are starting to brainstorm novel approaches, such as genetically silencing brain pathways critical for fertility and developing toxins that specifically target sperm and eggs. This summer, Michelson's foundation announced its first grantee, with more to follow. The scientific challenges are daunting, however, and some question whether such a product could actually solve the global dilemma of cat and dog overpopulation.

A walk on the wild side

The story of nonhuman contraception traces back to Billings, Montana, in 1971, when two cowboys walked into the office of a young Montana State University assistant professor named Jay Kirkpatrick. The U.S. Congress had just passed the Wild Free-Roaming Horses and Burros Act, which sought to prevent the often-brutal hunting of feral horses in the American West for pet food.

Although the cowboys applauded the principle of the legislation, they knew that without some sort of population control, wild horse numbers would soon explode. "They saw the train wreck coming years before it got here," says Kirkpatrick, now the director of the Science and Conservation Center, a Billings-based nonprofit dedicated to managing wildlife. "They came into my office—hats, boots, the whole 9 yards—and said, 'Can you make horses stop reproducing?'" Kirkpatrick was dumbfounded but intrigued.

"The concept of contracepting large wildlife was really off the screen," he says. "It hadn't been tried before."

Kirkpatrick first turned to human contraception—specifically, "the pill," a hormone-based approach introduced a decade earlier. Colleagues gave him a hard time. "I got laughed at a lot in the early days," he says. "I couldn't convince anybody that this was more than a harebrained idea."

Things started to change in 1977, when the Bureau of Land Management granted Kirkpatrick \$300,000 to test his hormone

idea in western horses. "All these people who had been snickering before were suddenly interested in wildlife contraception," he says. Over the next 10 years, Kirkpatrick showed that he could contracept wild horses with steroid shots that lasted through the breeding season. But catching the horses was expensive, and the hormones caused cancer in zoo animals. "The practicality wasn't there," he says.

So in 1988, Kirkpatrick says he "chucked everything out the window" and tried a new approach called immunocontraception. Originally developed for women, the idea was to administer a vaccine that would stimulate the production of antibodies against zona pellucida—the membrane that covers eggs—thereby preventing sperm from entering.

In humans, the approach proved less effective than the pill, but Kirkpatrick had great success in horses. He traveled to Assateague Island off the coast of Maryland and Virginia, which was dealing with its own impending horse overpopulation problem, and spent

Man's best friends?

About the time that Kirkpatrick hit upon the immunocontraception approach, Julie Levy was witnessing the homeless pet problem for the first time. As a veterinary student at the University of California, Davis, in the late 1980s, she walked past sickly feral cats every day on her way to class. Occasionally, the campus's public health and safety department would round them up and euthanize them. "As veterinary students who were trained to save animals, killing all of these cats

seemed very contradictory to what we were on campus to do," says Levy, now the director of a shelter medicine program at the University of Florida, Gainesville. So, with the faculty's permission, Levy and a group of students began trapping and surgically sterilizing the cats. "By the time we graduated," she says, "most of the cats on campus were neutered."

Levy's small program was part of a larger surgical sterilization movement begun in the 1970s. Estimates suggest that, by the beginning

of that decade, U.S. shelters were euthanizing more than 20 million cats and dogs each year. At the time, most vets considered spay/neuter surgery "unwarranted mutilation" and performed it on only about 10% of dogs and cats, says Andrew Rowan, the chief scientific officer of the Humane Society of the United States. But as feral dogs posed an increasing public health risk, animal-welfare groups began pushing for surgical sterilization. Today, most U.S. shelters spay or neuter every animal that leaves their doors.

The surgical sterilization movement has had a dramatic impact. "Feral dogs are now, in large part, a thing of the past in the U.S.," says Rowan, and rates

of euthanasia have dropped precipitously. Yet U.S. shelters still euthanize nearly 4 million healthy dogs and cats every year, he says, and about 30 million feral cats still roam the streets. Feral cats are also a huge problem in Australia, where some environmentalists claim they have hunted endangered species to extinction.

Feral dogs, on the other hand, tend to dominate in developing nations. Rowan says India alone is home to up to 35 million "street dogs," which in 2004 caused the vast majority of the country's 20,000

Online

sciencemag.org

Podcast interview
and reporter's
notebook.



Down and out. Feral dogs are a huge problem in developing countries, where they cause thousands of rabies cases.

months wading through marshes and forests, darting mares with the zona pellucida vaccine. "A year later, not a single foal was born," he says, and the vaccine showed no side effects. "The Assateague work changed everything."

That's when Kirkpatrick's phone started ringing off the hook. For the past 2 decades, he and colleagues have used the zona pellucida vaccine to contracept everything from urban deer to sea lions. The vaccine was so effective in so many species that when researchers asked to try it in cats and dogs, Kirkpatrick was sure it would work. It didn't.

human rabies cases. There's little funding for sterilization programs, he says, so "there's no way to take these dogs off the streets." China has also seen a spike in rabies cases and has responded with massive culling campaigns: City workers fan through towns, says Rowan, clubbing dogs to death by the thousands.

"We need to stop the carnage," says Rowan. "That's where the whole idea of a better contraceptive comes into play."

A decade after leaving vet school, Levy began looking into such a contraceptive. She had founded a few high-volume spay/neuter clinics for feral cats—called Operation Catnip—but "the cats were reproducing faster than we could sterilize them," she says. So Levy asked Kirkpatrick for some of his zona pellucida vaccine. She ran a small clinical trial in cats. But "it had zero efficacy," she says. Trials in dogs showed similar results. Levy says the antibodies the females produced did not bind to their eggs—and thus did not block sperm entry.

Undaunted, Levy turned to another approach that had proven successful in wildlife: a vaccine called GonaCon. Developed in 1994 by immunologist Lowell Miller at the U.S. Department of Agriculture's National Wildlife Research Center in Fort Collins, Colorado, the vaccine induces the body to make antibodies against the brain's gonadotropin-releasing hormone, which signals the production of various sex hormones. In field trials, Miller and colleagues contracepted deer, prairie dogs, and even kangaroos. Levy found that the vaccine also worked well in cats: A single injection contracepted males and females for up to 5 years, although the effect diminished over time. Other groups tried the vaccine in dogs but stopped trials after the injection caused a painful reaction.

In 2004, Levy also began working with a sterilant called ChemSpay. Loretta Mayer, an ovarian physiologist at Northern Arizona University in Flagstaff, had helped develop the product—a chemical that destroys female eggs—and had used it to sterilize feral dogs on a Navajo reservation. Levy saw results in cats, too, but the product required multiple injections over several

days, making it impractical for hard-to-catch feral animals.

Levy and Mayer worked to improve the efficacy of GonaCon and ChemSpay, respectively, but both soon ran short of money. "Animal work is horrendously expensive," says Levy. Each research cat costs her \$800—and \$5 a day to feed and house. She and Mayer scraped together small grants, but neither could find a large funding agency to support the research. "There were times between grants when I was paying for the cats myself for a year," says Levy.

lion in grants and a \$25 million prize for the first team to develop a viable product. "I had never thought about this problem before," says Ja, "but I was inspired by the challenge." He brainstormed with some colleagues over dinner and came up with an idea that he thought might work.

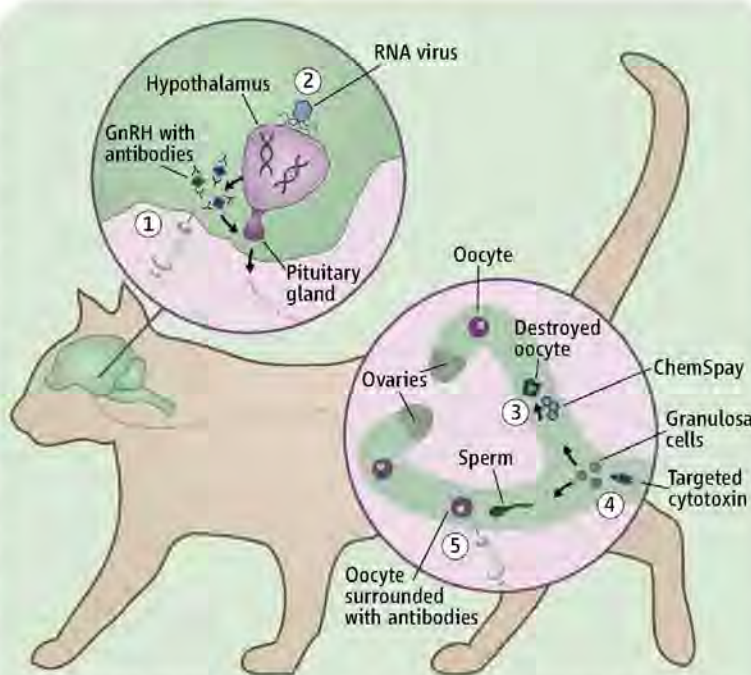
The awards are the brainchild of Michelson, a retired spinal surgeon and one of the richest people in the United States, thanks in part to a \$1.35 billion settlement over surgical devices he invented. An animal lover who has also donated millions to humanitarian causes, Michelson says he was saddened

and frustrated by current animal-control efforts. "The amount that municipalities in the U.S. spend to catch, house, and kill our pet cats and dogs is staggering," he says. "Surely we should be able to come up with a more cost-effective and humane approach."

Last year, Michelson's Found Animals foundation created a review board of scientific advisers and started seeking proposals. The response has been overwhelming. To date, the foundation has received more than 80 pitches—from academics, physicians, and industry scientists, many of whom have no background in companion-animal research. "There's a lot of very bright people out there who haven't applied their research direction to dogs and cats, in part because there's been no money," says Found Animals scientific director Shirley Johnston, a former veterinarian with a Ph.D. in clinical reproduction.

"We've seen some very impressive ideas." (And some that were not so impressive. One proposal described a kitty chastity belt, complete with blueprints.)

Ja sent in his proposal, and he was one of nearly 30 scientists asked to submit a full grant application. His idea draws heavily on his work in fruit flies, for which he has designed proteins that target specific receptors involved in aging. For his Michelson project, Ja wants to target Sertoli cells and granulosa cells instead. In mammals, these gonad-specific cells foster the development of sperm and eggs, respectively. Ja hopes that by attaching a cytotoxin to his targeting proteins, he could essentially create a missile that would seek out and



Sterilization strategies. Researchers are looking into a number of ways to permanently sterilize cats and dogs without surgery, including: (1) a vaccine that would block the release of sex hormones, (2) a virus that would genetically silence fertility pathways, (3) a chemical that would destroy eggs, (4) a targeted cytotoxin that would destroy cells necessary for the production of sperm and eggs, and (5) a vaccine that would block sperm from entering eggs.

Nonsurgical sterilization research stuttered and slowed. An Australian group working on cat contraception abandoned its studies entirely when funding ran out. And then Gary Michelson entered the picture.

A shot in the arm

In November of 2008, postdoc William Ja was taking a break from his lab work at the California Institute of Technology in Pasadena when an ad in a scientific journal caught his eye. Seeking to minimize shelter euthanasia, a Los Angeles-based nonprofit called Found Animals was announcing \$75 million toward the development of a nonsurgical sterilant that would work in male and female cats and dogs—\$50 mil-

destroy these cells and cause permanent sterilization. "The basic idea is to treat cells that are critical for reproduction as cancerous," he says.

The first applicant to actually receive Michelson grant money is Beverly Davidson, a neuroscientist and the associate director of a gene-therapy center at the University of Iowa in Iowa City. Davidson's project builds on her lab's use of RNA interference to treat neurogenetic diseases like Huntington's. Like Ja, she's pursuing a targeted approach—but her weapon is genetic: Davidson's lab plans to design a virus that would deliver an RNA interference payload to regions of the brain involved in fertility, genetically silencing critical pathways. The virus would hang out in these brain cells indefinitely, resulting in permanent sterilization. "It would be like a switch we turn off," she says.

Levy and Mayer have also applied for Michelson grants, hoping that the cash infusion will help them optimize GonaCon and ChemSpay for dogs and cats. "Our excuse for not having a product after 30 years of research into contraception is that there's never been enough money or enough people with interest in this field," says Levy. "All of that has now been wiped away with the stroke of a pen."

Michelson says he hopes to see a product on the market within 10 years. But is such a product realistic?

Pitfalls in the past

Any research team embarking on the path of companion-animal sterilization would do well to heed the lessons of Neutersol. A formulation of zinc gluconate—the same compound often found in anti-cold and flu lozenges—the product was designed to be injected directly into the testicles of dogs, where it causes testicular atrophy. Briggs says ACC&D's lack of funding slowed U.S. Food and Drug Administration approval, and veterinarians were hesitant to use the product when it finally came on the market in 2003. What's more, Neutersol was not much cheaper than traditional spay/neuter surgery, so shelters had little incentive to adopt it. Disagreements over how to market the product forced it off U.S. shelves in 2005, although some Latin American countries still use it.

Michelson says he has designed his awards to avoid these pitfalls. To ensure that a promising technology makes it to market quickly, his foundation will "finance and support commercialization of the prize-winning product," including funding clinical trials and helping with regulatory



Zero efficacy. Julie Levy gave the zona pellucida vaccine to these research cats, but it didn't work.

approval. Ja says that's been a huge incentive for him: "As a basic researcher, it's very appealing to think that if my work gets somewhere, I don't have to build a team all by myself and push this out."

Michelson also says he'll work to make the product cheap, subsidizing its cost if necessary. "If it's going to get widespread traction in the developing world—and even in cash-strapped U.S. shelters—it's going to need to be a few dollars a dose," says Levy.

Still, some question whether Michelson's scientific criteria are too rigorous. The prizewinning product must cause permanent sterilization, for example, but Levy says even a temporary contraceptive could dramatically reduce the number of feral cats, because most don't live more than 3 to 4 years. What's

more, Cassandra James, a viral immunologist who has researched nonsurgical sterilants at Murdoch University in Western Australia, says she doubts any single product will work in both males and females, dogs and cats: "I think it's a Holy Grail that will probably never be achieved." Michelson says his foundation is "willing to consider applications for grant funding that may not address all criteria but have the potential to significantly impact the problem."

Levy and others also caution that even a perfect product will not eliminate cat and dog overpopulation. People still need to be responsible pet owners and spay/neuter their animals, for example. "There isn't one intervention that's going to solve this problem," says Levy. Michelson is optimistic, however. Citing data from high-volume spay/neuter programs, he says that if the prizewinning product could lower the number of animals coming into shelters by half, the euthanasia rate would drop by more than 90%.

Ja will find out in November if he'll be receiving Michelson funding for his cytotoxin-targeting project. Even if he doesn't, he says he's been so inspired by the problem that he may dedicate some of his start-up money to the idea once he heads his own fruit fly lab in a few months.

Back in Oak Hill, David Fuller is doing some anxious waiting of his own. "When I first heard about the Michelson Prize," he says, "I said, 'Bingo! This is just what we need.'" He's even volunteered his feral cats for clinical trials. "If we could put a sterilant in the feed that we put out for these cats, we could control the population," he says. "It would be a lifesaver."

—DAVID GRIMM



Big spender. Gary Michelson is offering \$75 million toward the development of a nonsurgical sterilant for cats and dogs.

ASTRONOMY

Scrambling to Read the Meaning Of the Sky's Most Ancient Flare

This spring, a seemingly routine gamma ray burst triggered a worldwide race to catch a glimpse of the early universe

On 23 April, astrophysicist Nial Tanvir had just dropped his daughter off at school when an automated text message appeared on his cell phone. NASA's Swift satellite had just detected a gamma ray burst (GRB)—a brief flash of high-energy radiation emitted by a star collapsing to form a black hole. "Oh boy, here we go again," Tanvir, a researcher at the University of Leicester in the United Kingdom, recalls thinking.

Tanvir's mix of excitement and ennui is familiar to GRB astronomers, who receive two or three burst alerts a week. They must respond quickly by pointing ground-based telescopes at the burst to observe its afterglow, which fades away in a matter of hours or days. Most GRBs turn out to be from the nearby universe and do not yield new insights. A coveted few, however, went off billions of years ago and provide a window on the enigmatic early universe. When Tanvir read the alert, he knew his team was in for a frenzy of observation and analysis that was more likely to produce a humdrum result than an interesting one.

As it turned out, GRB 090423 was the most distant burst astronomers had ever seen. In two papers on the arXiv preprint server (arxiv.org), Tanvir's group and a competing team led by Italian astronomer Ruben Salvaterra report that the burst's redshift of 8.2 means that it went off a mere 625 million years after the big bang, when the universe was less than 5% of its current age. The photons it spewed into space traveled for more than 13 billion years before reaching Earth.

Not only did the burst shatter the previous record for the farthest object seen—a galaxy at redshift 6.96, discovered in 2006—but it also proved that the universe came alive with stars within a few hundred million years of the big bang. "It brings us close to that magical point of first light," says Volker Bromm, an astrophysicist at the University of Texas, Austin. "We don't have to get much farther to catch the earliest stars." The discovery of GRB 090423 and the ensuing race to publish observations also offer a glimpse into 21st-century astronomy—a high-stakes pursuit in which communications

networks make possible worldwide, round-the-clock collaborations, and pressures for cooperation and competition often come into simultaneous play. "This is extreme astronomy," says Don Lamb, a theoretical astrophysicist at the University of Chicago in Illinois.

All-night dash

Shortly after Tanvir received the alert, he was conversing via e-mail with his colleagues at the Joint Astronomy Centre (JAC) in Hilo,



Far out. A 13-billion-year-old explosion (center) riveted astronomers.

Hawaii, who had already started planning observations using the United Kingdom Infrared Telescope (UKIRT) near the summit of Mauna Kea. The good news was that night had only just begun in Hawaii—it was 10 p.m.—and the burst had gone off over the Pacific Ocean, which meant observations were possible. The bad news was that it was a windy night with gusts of up to 80 kilometers an hour blowing across the mountain. Opening the telescope's dome would subject the instrument to wobbling that would make it difficult to get any useful images.

"We were in fact closed for the night when we got the alert," says Tom Kerr, one of the observers at JAC. But he and his colleagues decided to take a chance. "Against our better judgment, we will try it," Kerr e-mailed

Tanvir, starting the observation some 21 minutes after the burst. "We observed the target for 20 minutes, and then the wind got too much for us," he says.

Thousands of kilometers away, sitting in an auditorium listening to talks about the future of U.K. astronomy, Tanvir kept glancing at his laptop in anticipation of the first images. He was also in touch with scientists operating Gemini Observatory's 8-meter North telescope, also on Mauna Kea, which had begun taking observations in the optical band within minutes of the burst.

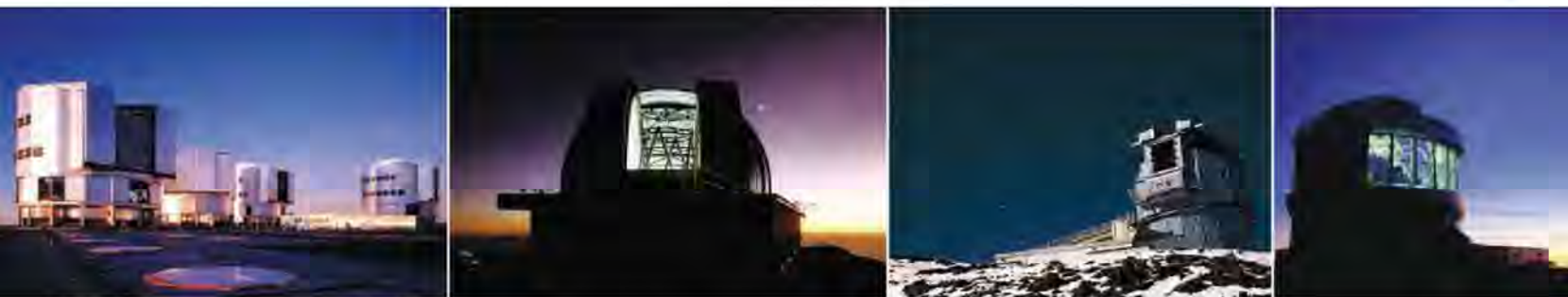
The burst appeared as a fuzzy spot in near-infrared images taken by UKIRT but didn't show up in optical images taken by Gemini. To Tanvir and others, this was a clue that it had occurred at a high redshift. Visible light from the burst had shifted to the near-infrared, and ultraviolet light—which should have shifted to visible wavelengths—had been absorbed by intergalactic hydrogen, causing the burst to vanish in the optical band.

By noon, Tanvir says, "we knew we were looking at something very interesting." He and Andrew Levan, an astronomer at the University of Warwick in the United Kingdom, grabbed lunch from the buffet table and found a quiet spot outside the auditorium to discuss the data. "We weren't going back to listen to any more talks," Tanvir says.

First they announced the UKIRT observations on the Ground Control Network (GCN), a NASA e-mail list that had circulated the automated burst alert. The GCN system serves as a bulletin board for the GRB community, enabling astronomers to coordinate follow-up observations. It also functions as a logbook and timeline of discovery. In flagging the burst for other astronomers, Tanvir and his colleagues had planted their own flag, too.

Across the Atlantic, Harvard University's Edo Berger and Pennsylvania State University's Derek Fox and Antonino Cucchiara were crunching new data taken by an infrared imager mounted on Gemini's North telescope starting 75 minutes after the burst. The objective was to confirm that the lack of an optical signal was indeed due to high redshift rather than to dust blocking visible light emanating from the burst. About 4 hours after Tanvir's circular on GCN, Berger and his colleagues posted the first estimate of how distant the burst was: a redshift of 9. Later that evening, they would revise the estimate to somewhere between 7 and 9.

More-detailed information and a definitive measurement of redshift could come only from spectroscopy. For Tanvir and his



collaborators, that meant a second night of observations, this time using the European Southern Observatory's 8.2-meter Very Large Telescope (VLT) in Chile.

Time was of the essence not only for getting the data but also for analyzing it to solidify the claim to discovery. And so, after debating whether to sleep at all, Tanvir went to bed, setting the alarm for 1:30 a.m. when the night would be starting in Chile. When he woke up, he tiptoed over to his spare bedroom and logged on to his computer.

There was troubling news: A technical problem at VLT had caused a delay. "For some time, it felt like that might scupper the situation," Tanvir says. Then, 17.5 hours after the burst, the telescope began taking spectra using the Infrared Spectrometer And Array Camera (ISAAC). Meanwhile, researchers at the Max Planck Institute (MPI) for Astrophysics in Garching, Germany, had posted a more definitive value of redshift—about 8.0—based on images taken 15 hours after the burst by a 2.2-meter telescope owned by MPI and ESO at the La Silla Paranal Observatory in Chile. The Italian group—led by Ruben Salvaterra, Guido Chincarini, and others at the Italian Institute of Astrophysics in Merate—was racing Tanvir's group to finish the spectral analysis. Using the 3.6-meter Telescopio Nazionale Galileo on La Palma in the Canary Islands, the researchers had begun taking near-infrared spectra of the burst's afterglow 3 hours before VLT.

When Tanvir started analyzing the VLT data, dawn was breaking over Cambridge. He saw a GCN circular from the Italian group, posted shortly after 4 a.m. It was the first spectroscopic result about the burst, reporting a redshift of 7.6. At 8:20 a.m., a bleary-eyed Tanvir posted the results of his group's spectral analysis showing a redshift of about 8.2, which turned out to be more accurate.

Splitting the difference

Even though every group that collects data on a burst could choose to publish independently, astronomers know they can increase their

chances of publishing in a high-profile journal by combining observations. Strategic alliances start to form even while the observations are being made, says John Nousek, an astrophysicist at Pennsylvania State University, University Park, and one of 45 co-authors on the Salvaterra paper. Because GRBs are such a community event for astronomers, he says, there's a very public race to publish. "Of course, ego plays a role," he says.

For Tanvir and Salvaterra, the race to publish began as soon as the race to analyze observations had ended. Tanvir quickly began writing a draft, forming an alliance with the different groups he

Burst watchers. Left to right: The Very Large Telescope, United Kingdom Infra-Red Telescope, Telescopio Nazionale Galileo, and Gemini Observatory.

the papers were, how unique the data sets were," says Gehrels, who eventually joined the Tanvir paper while assigning some of his colleagues to Salvaterra's team. After weeks of discussion, the two sides agreed to keep their papers separate but attempt to publish them simultaneously. On 9 June, the two papers appeared together on astro-ph, the astrophysical section of the arXiv preprint server, with a note indicating that each had been submitted to *Nature*.

The astro-ph papers reach similar conclusions about the burst's redshift and significance. The Salvaterra paper makes the additional inference that the star that collapsed to produce the burst contained elements heavier than hydrogen and helium. That suggests it formed well after the first stars in the universe—made entirely of hydrogen and helium—had had time to synthesize heavier elements and spew them into the galactic medium.

Although Tanvir agrees that the star could not have been a first-generation object, he says the spectroscopic data are too sketchy to support any conclusions about its composition. Sandra Savaglio, a researcher at the MPI for Extraterrestrial Physics in Garching, Germany, is skeptical as well. "You can't say anything about the metallicity [composition] based on these spectra," she says.

The next time Swift detects a high-redshift burst, astronomers hope, telescopes on the ground will respond even faster, capturing data that will help paint a more vivid picture of the early universe. "There were no successful attempts to take spectra on the first night, which is a real pity," says Lamb. But he's optimistic that nature has more opportunities in store; and that not too far in the future, light from an even more ancient collapsing star will quicken the pulse of observers and gladden the hearts of theorists.

—YUDHIJIT BHATTACHARJEE



Friendly rivals. Salvaterra (left) and Tanvir agreed to publish their papers together.

had been communicating with, including the researchers from Garching. Three days after the burst, he got an e-mail from Chincarini suggesting that the two groups work together.

According to Tanvir, Chincarini spelled out one condition: An Italian astronomer would have to be made first author of the paper. Chincarini's implicit argument, Tanvir says, was that "their spectrum was obtained a few hours before us." But "we could argue that we got the correct measurements first," he says. Tanvir declined the offer.

Neil Gehrels, an astrophysicist at NASA's Goddard Space Flight Center in Greenbelt, Maryland, and principal investigator for Swift, attempted to resolve the differences and have one paper. "We had e-mails and phone calls to discuss who was first, how far along

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LETTERS

edited by Jennifer Sills

Tenure: Where to Draw the Line

THE ARGUMENT THAT UNIVERSITIES AREN'T BUSINESSES ("TENURE AND THE FUTURE OF THE UNIVERSITY," D. Clawson, Education Forum, 29 May, p. 1147) has a great deal of traction among faculty members. However, it is ludicrous to suggest that running a university efficiently is possible without applying some hard-nosed concern for maximizing revenue and minimizing costs. Perhaps those committed to the continuance of the tenure system should consider that the definition of academic freedom need not encompass academic inactivity. If personnel decisions are left in the hands of faculty members, surely the "professionalism" mentioned by Clawson is sufficient to ensure the free speech and creativity of the university even without a tenure system. Understood this way, it may be that faculty members should truly draw a line in the sand at the

retention of the right to make appointment decisions for academic personnel, not at the continuation of tenure.

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Tenure: Expiration Time

IN THE EDUCATION FORUM "TENURE AND THE FUTURE OF THE UNIVERSITY" (29 May, p. 1147), D. Clawson used several statements as arguments for tenure that were in fact unfounded or unrelated to the issue of tenure.

Clawson proposed that when administrators cut costs by increasing the percentage of non-tenure-track and part-time faculty positions, the process of teaching becomes a process of content delivery, teaching to the test, and delivering a standard curriculum determined from above. There is no connection between these two scenarios. I have a full-time teaching position at a for-profit college

and a part-time teaching position at a community college. Neither position is tenure-track. Both colleges have programs in place to help all faculty develop teaching methods, creative lesson plans, and sensitivity to students' learning styles.

Content delivery and teaching to the test are unfortunately all too common, but they are unrelated to issues of tenure or employment status. Arguably, without the incentive of a need to prove themselves daily, tenured faculty may be more likely to resort to such practices.

Clawson's references to professionalism were also misdirected. The term "professional" applies as much to non-tenure-track and part-time faculty as to tenured faculty. It also applies equally to those engaged in many endeavors outside of academia. The term in no way implies an exclusive right to self-evaluate or self-police. All professionals, including all faculty, are accountable to others and therefore subject to outside evaluation.

Clawson pointed out that first-year students are less likely to return if their courses are taught by part-time faculty. This comparison between full-time and part-time faculty is unrelated to the issue of tenure. Clawson also noted that, given a choice, faculty prefer jobs

in the tenure system. The implication was that the tenure system is inherently superior. However, it is more likely that a preference for such a position simply reflects a preference for greater job security and comfort.

The elitist view that tenured faculty are somehow above scrutiny, have a more altruistic vision of a larger good than others, and are the exclusive champions of education, is a view whose time has expired. It is time for the tenure system to expire as well, and to move forward with a system in which all faculty must prove themselves daily. This system works efficiently and fairly in other professions and could work efficiently and fairly in the academic professions as well.

KENNETH R. GORDON

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Tenure: Incentivize Faculty

IN HIS EDUCATION FORUM "TENURE AND THE FUTURE OF THE UNIVERSITY" (29 May, p. 1147), D. Clawson makes salient points about the damaging effects of a permanent untenured faculty underclass, but he understates the role that many tenured and tenure-track faculty play in supporting this disturbing trend. When unprotected faculty teach and tenured faculty focus on research and departmental decision-making, students are less likely to be prioritized. This occurs despite national calls for greater scientific literacy and a broadening of participation in science.

Tenured and tenure-track faculty as well as university administrators need an incentive to meet student needs and to value those faculty who provide teaching services. A simple solution would be to tie a university's overhead rate on federal grants to the percentage of teaching services provided by tenured and tenure-track faculty. In such a system, a department delivering 75% of its teaching services with non-tenure-track faculty would receive only 25% of the normal overhead payment on the grants of its faculty.

Such a system would give both tenured and tenure-track faculty and administrators a financial incentive to extend tenure to more of their colleagues and to reevaluate departmen-

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 3 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.



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1506



Ferromagnetic ordering
of cold atoms

1507

tal decisions to farm out large introductory courses to non-tenure-track faculty. The balance of funds could be placed in a national fund reserved for professional development and research for non-tenure-track faculty, fulfilling a serious need, as these faculty generally have no access to the regular research funds needed to remain active in research and to escape the academic underclass.

SADREDIN CYRUS MOOSAVI

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Response

THE LETTERS BY GORDON AND MOOSAVI raise an important issue: Discussions about tenure can focus on either the tenure system

or the individuals who are and are not in tenure-system positions. My Education Forum focused on the larger system, with an emphasis on the reasons for, and consequences of, the continuing movement away from the tenure system. Gordon and Moosavi, in different ways, argue (correctly) that the dynamics for the larger system do not necessarily apply to each individual.

I argue that a strong tenure system is vital if universities want to emphasize free speech and creativity, and note that the tenure system is strongest at leading research universities and liberal arts colleges and weakest at for-profit colleges and community colleges. That certainly does not mean that all individuals with tenure-system positions promote and uphold the values and practices of student and

researcher creativity. Nor does it mean that non-tenure-system faculty abjure these values and happily engage in "content delivery" and teaching to the test.

The issue here is not moral values but structural position. You can be moderately well paid, teach two courses a semester, know that you can stay for your lifetime and expect to do so, have full control over the syllabus and readings for your courses, be encouraged to develop new course offerings, and be actively involved in the governance of your institution. Alternatively, you can be teaching eight courses a semester scattered over three different institutions, never know where (or if) you will be teaching the next semester, not have an office, not be involved in decisions about the institution, have to use a syllabus and readings selected by someone else, and be earning far less than the average holder of a bachelor's degree. You will most likely develop a different set of attitudes and behaviors as the result of occupying a different place in the system. The practice will necessarily be different even if the goals and values start out the same. The point is to develop systems that encourage and protect all faculty.

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Gordon reports that in both of his teaching situations, the college predetermines his course syllabi. That is rarely the case at highly selective research universities and liberal arts colleges. Gordon also reports that he nonetheless exercises creativity and encourages it in his students. I absolutely believe that faculty in non-tenure-system positions seek to be creative, but the structural conditions limit that creativity, as in the imposition of a standard syllabus.

Moosavi looks at the other side of the coin: Tenure-system faculty often cooperate in this process, seeking to guarantee their future advancement by shunning low-status activities and embracing high-status activities. In many cases, that means that they avoid teaching introductory students, or avoid teaching altogether. Moosavi points to an important problem, but I believe that it is not a consequence of the moral failures of tenured faculty, nor of the tenure system, but rather of the attack on the tenure system and the emergence of a two-tier faculty. The structural conditions encourage and reward this behavior. Moosavi suggests a structural change—tying university grant overhead rates to the percent of students taught

by tenure-system faculty—to address the problem. I applaud the effort to develop such structural solutions.

DAN CLAWSON

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Increase Grants, Too

THE NEWS FOCUS STORY "RESHUFFLING graduate training" (J. Mervis, 31 July, p. 528) suggests that a change in graduate student funding from grants to fellowships and traineeships will increase the independence of young scientists and boost U.S. science. We agree, but caution that shifting resources to fellowship programs could fail to produce desired results without additional increases in direct support for graduate student research.

Our graduate educations are funded by a U.S. Department of Agriculture National Needs Traineeship and a U.S. Department of Energy Graduate Research Environmental Fellowship. Similar to fellowship programs funded by NSF, NIH, or the EPA, these training programs are prestigious but provide little or no research funding. Accordingly, recipients often work on ideas that are closely affiliated with

existing grants rather than developing independent research. Moreover, the effectiveness of NSF Graduate Research Fellowships may also be limited by eligibility requirements that exclude students with master's degrees. Students with a master's degree may be more prepared for independent research compared to counterparts with a bachelor's degree.

Nonetheless, training and fellowship programs can spur independence. We used our fellowships as a platform to compete for research grants. Research grants that we received from NSF and NOAA provide independence to develop our own ideas and experiments. An increase in research fellowships together with a substantial increase in research grants would be a more effective way to encourage graduate student creativity, autonomy, and success.

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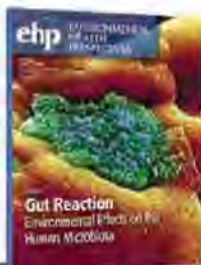
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Stable Funding Is Key

IN THE NEWS FOCUS STORY "RESHUFFLING graduate training" (31 July, p. 528), J. Mervis describes Roald Hoffmann's proposal to dramatically shift U.S. federal research funding from principal investigator (PI)-controlled grants to graduate student fellowships. However, Mervis does not mention an important argument for Hoffman's proposal: the importance of funding continuity during the entirety of a student's Ph.D. education.

As a former graduate program director, I have observed first-hand that stable funding for the duration of a student's Ph.D. studies can affect both the timely completion of the Ph.D. and the student's likelihood of remaining in graduate school. When students (and their PIs) experience funding gaps, responses vary dramatically, even within a given university campus. Some programs leave the student entirely without funding. Other programs provide bridge funding or a teaching assistantship, possibly of finite duration or with strings attached. Even if the student obtains support from another sponsored research grant, such a switch can have serious implications for the

content and direction of the student's studies.

As a PI, I would gladly give up some amount of funding in return for a secure 5 years of funding for a promising new Ph.D. student to pursue his or her Ph.D. studies. I was pleased to read that senior NSF officials at least consid-

ered such proposals in the past and would encourage both NIH and NSF to explore such mechanisms in the future. **ROBERT J. BUTERA**

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TECHNICAL COMMENT ABSTRACTS

COMMENT ON "The Dynamic Control of Kiss-And-Run and Vesicular Reuse Probed with Single Nanoparticles"

Björn Granseth, Benjamin Odermatt, Stephen J. Royle, Leon Lagnado

Zhang *et al.* (Research Articles, 13 March 2009, p. 1448) reported that synaptic vesicles usually release neurotransmitter through a kiss-and-run mechanism occurring within 1 second but that full collapse of the vesicles becomes more prevalent with repeated stimuli. We report that the kinetics of vesicle retrieval do not change during a stimulus train, with endocytosis occurring in 10 to 15 seconds.

Full text at www.sciencemag.org/cgi/content/full/325/5947/1499-b

RESPONSE TO COMMENT ON "The Dynamic Control of Kiss-And-Run and Vesicular Reuse Probed with Single Nanoparticles"

Qi Zhang, Yulong Li, Richard W. Tsien

Granseth *et al.* argue that vesicle retrieval at hippocampal synapses is fully accounted for by a single mode of endocytosis. However, their assay focused on readily releasable pool vesicles (RRP), not RRP + reserve pool vesicles in tandem, and therefore cannot detect pool-dependent changes in vesicle-retrieval kinetics during a stimulus train. Using a probe similar to theirs, we observed rapid vesicle retrieval consistent with kiss-and-run fusion.

Full text at www.sciencemag.org/cgi/content/full/325/5947/1499-c

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HISTORY OF SCIENCE

Ecology Emerging

Matthias Glaubrecht

The history of science allows researchers to learn from the past, as the awareness of our intellectual roots provides a basis for anticipating future goals and developments. However, foretelling or influencing the future are motives often uncongenial to historians, whereas scientists' interests in the past are, as Mary Winsor has so vividly demonstrated (1), usually intimately linked to their interests in the future. In this respect, I plead guilty. My passion for the past and interests in Lynn Nyhart's *Modern Nature*, its historical figures, and her discussions of developments in natural history in late-19th- and early-20th-century Germany (in particular at Berlin's Museum für Naturkunde) are oriented toward the future of organismal biology—especially as it may be carried out by curators in natural history museums.

One of my heroic forerunners and central to Nyhart's rich account is Karl August Möbius (1825–1908). Although his varied contributions are neither widely known nor acknowledged today, Möbius was one of the most important and influential zoologists of his time. His concurrent scientific and popular writings and mutually reinforcing research and civic activities helped spread his innovative ideas (2). The most important and fundamental for both ecology and marine biology was his novel concept of "biocönose" or *Lebensgemeinschaft*, the biotic community. These biological societies, as he often called them, were characterized by the dependence of their members on one another as well as their physical conditions of existence. Based on Möbius's insightful studies of oyster cultures (3), his biocönose became a foundational idea of German ecology. Möbius also implemented innovative research, curation, and exhibition practices, first as director of Kiel's Zoological Museum and after 1887 as head of the "pinnacle of German natural history," Berlin's university museum.

Nyhart (a historian of science at the University of Wisconsin) has previously discussed Möbius's "unlikely career" (4). Starting as an elementary school teacher, he became a researcher, university professor, and museum director and moved from nat-

ural history through economic zoology to ecological theory and museum reform. In *Modern Nature*, Möbius serves Nyhart as an instructive example of a scientific career while she traces the populist beginnings of animal ecology and its development into an academic discipline. Möbius played a pivotal role because his ideas and career were central to the rise of what Nyhart calls the "biological perspective": an approach that views the organism as a living being embedded in nature, whose survival depends on its abilities to interact successfully with both its physical environment and neighboring organisms.

As Nyhart explains, placing the term in its late-19th-century context, this perspective contrasted starkly with systematics, which had been the main emphasis of natural history since Linnaeus's time. Most museum researchers focused on the similarity and (especially after Darwin) relatedness of organisms; curators generally paid less attention to functional relations among organisms, their physical environments, and their geo-



Museum-based reformer. Karl August Möbius (Ernst Hildbrand, oil, 1895).

Modern Nature

The Rise of the Biological Perspective in Germany

by Lynn K. Nyhart

University of Chicago Press, Chicago, 2009. 437 pp. \$45, £31. ISBN 9780226610894.

graphic and ecological places in the world. Here Möbius made a difference visible to the public. For example, on becoming director of the Berlin museum, he immediately arranged displays of an oyster bank and a tropical reef. These offered a lively, attention-getting alternative to the former endless parade of objects and species in museums that left lay visitors bored

and overwhelmed. Thus it is very appropriate that Nyhart portrays Möbius and a few similar-thinking contemporaries as successful popularizers of ecology.

In addition to discussing how this new brand of biologists attended to the living organism in its natural setting, Nyhart explores the relation between the emergence of modern society and the construction of a modern vision of nature. She argues that profound and rapid reorganization of German society at the time of industrialization and urbanization drew attention to the roles of community relationships and physical environments in both nature and society. As a result, the biological perspective developed alongside an awareness of the environmental degradation. She also offers a compelling case that new cultural institutions of the public sphere (such as museums, civic botanical and zoological gardens, secondary schools, and libraries) were at the forefront of the rise of populist, community-based ideas that eventually led to ecological thought in academic science. As she convincingly shows, ecology has its roots in Germany outside the universities. It did not develop in the elite realm of academic science but in the vibrant civic realm of cultural institutions, inhabited by schoolteachers, museum curators, zookeepers, taxidermists, writers, amateur enthusiasts, and nature protectionists. Rarely before has the art of making animal exhibits for popular education looked so important. With her fresh perspective that this part of *Naturkunde* (nature studies) was not elite zoology in Germany, *Modern Nature* joins earlier accounts by Andreas Daum (5) and Susanne Köstering (6) as an exemplary contribution to the cultural history of science.

As in her earlier book on the foundations of animal morphology (7), here Nyhart focuses on German researchers and institutions. She discusses Karl Kraepelin in Hamburg, Philipp Leopold Martin in Stuttgart, and a few others, but her emphasis is on Möbius and those professionally related to him—e.g., the schoolteacher Friedrich Junge (who

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turned Möbius's community concept into a wider program for school reform) and the Berlin museum curator Friedrich Dahl (who developed Möbius's ecological ideas into ecological animal biogeography). This German perspective offers a broader understanding of the foundations of ecology, with Nyhart explicitly providing "an alternative to the Anglo-American orientation that has dominated English-language histories of ecology." I found that her wonderful and important story of this epoch of German natural history sub-

stantially expands our picture of biology in the late 19th and early 20th centuries. *Modern Nature* not only adds another layer of complexity to that canvas, its new angles on the story facilitate our understanding of the ways science got done. The book reinforces Winsor's plea that historians not give up on the idea that investigations into the past are both anchors and useful guides to the future.

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NATURAL HISTORY

Many Reflections on Birds

Devorah Bennu

Although thoughtful and eloquent, Jeremy Mynott's *Birdscapes: Birds in Our Imagination and Experience*, like its subject, is elusive. Mynott (a long-time bird enthusiast and former head of Cambridge University Press) uses birds as an anchor to reflect on the intersections among nature, art, and culture. He investigates how knowledge is constructed and communicated and how it may be constrained by both semantics and methods of classification. Mynott's reflective yet unconventional approach includes citing sources ranging from Roman-tic poets and Japanese haiku masters to scientists, sports figures, and even Monty Python. The book's breadth makes its character as difficult to capture as a wild bird. Mynott covers such topics as why birds sing, the perceived value of rarities, how we name birds, and the relationship between birds and the landscapes they inhabit. Perhaps a consideration of an individual chapter can illuminate the essence of the book.

In the chapter "Seeing a Difference," Mynott explores the importance of seemingly minor details. To illustrate this premise, he begins with a personal anecdote that will especially appeal to birders: British Birds Rarities Committee chair Peter Grant is in the Scilly Isles, just off the coast of Cornwall, where he spots one shorebird in a large flock. Within seconds, he confidently identifies it as a very lost (and thus very rare) semipalmated

sandpiper (*Calidris pusilla*) from North America. To do so, Grant relied on recognition honed through decades of practice in learning to see.

Like Grant, all birders—and all scientists—must understand variation and recognize variants. Most birders concentrate on variation between species, identifying birds as representatives of species rather than as individuals. But individual differences must always be in the back of their minds when looking at birds; otherwise they will not know whether a given bird is a variant of one species or is a different species. As the author wryly notes, "Many rare birds are undoubtedly overlooked just because the common ones are underlooked." This knowledge allowed Grant to spot that one rare bird in a crowd and immediately recognize that it was not just another common "peep."

But perceiving differences depends on our brains' ability to decipher detailed environmental inputs to construct something believable. In addition, it is important to remember the brain's ability to deceive itself to fulfill expectations, as when mistaking a cowpat for a night hawk (a story recounted by the author). Noticing details provides a crucial beginning to understanding which variations are specific to an individual versus those that define a species (or even a cowpat).

Recognizing variation is important to scientists as well. Physical variations between individual birds can be as distinctive as human fingerprints—something that has been meticulously documented by several research orga-



Swallows in flight. Detail from the "spring fresco," Room Delta 2, Akrotiri, Thera (circa 1650 BCE).

nizations that study individual life trajectories. This ability to perceive variation is especially important when studying hybrids, subspecies, cryptic species, and so-called "ring species" among already challenging-to-identify birds such as gulls, wagtails, and even some species of ducks and tits. Mynott points out that the species concept also generates confusion: "the idea of a species is itself not an entirely hard-edged one, a fact that produces employment for scientists and may induce neuroses in listers."

But even experts make mistakes. Despite the author's thorough attention to detail, there are lapses in accuracy that might bother some readers. For example, the author mistakenly refers to the Baltimore oriole (*Icterus galbula*) as the northern oriole, taxonomy that was abandoned by the American Ornithologists' Union in 1995. There are also occasional errors in scientific names.

Like Grant's rare sighting of that semipalmated sandpiper, Mynott's book is a rare philosophical exploration of our multifaceted experience with birds: why we are attracted to them, how we encounter and describe them, and their significance in our lives. Despite its occasional inaccuracies, *Birdscapes* will appeal to readers who luxuriate in literature and who enjoy nature and especially birds.

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Birdscapes

Birds in Our Imagination and Experience

by Jeremy Mynott

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Princeton, NJ, 2009.
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The reviewer writes the blog Living the Scientific Life (Scientist, Interrupted). Web site: <http://scienceblogs.com/grrlscientist/>

Biodiversity Conservation and the Millennium Development Goals

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The Millennium Development Goals (MDGs) are designed to inspire efforts to improve people's lives by, among other priorities, halving extreme poverty by 2015 (1). Analogously, concern about global decline in biodiversity and degradation of ecosystem services (2) gave rise in 1992 to the Convention on Biological Diversity (CBD). The CBD target "to achieve by 2010 a significant reduction of the current rate of biodiversity loss" was incorporated into the MDGs in 2002. Our lack of progress toward the 2010 target (3, 4) could undermine achievement of the MDGs and poverty reduction in the long term. With increasing global challenges, such as population growth, climate change, and overconsumption of ecosystem services, we need further integration of the poverty alleviation and biodiversity conservation agendas.

The links between poverty and the environment are, unsurprisingly, complex (5, 6) (Fig. 1). Some attempts have been made to identify a relation between development and biodiversity, but these have yielded mixed results (5). Action is urgently needed to identify and quantify the links between biodiversity and ecosystem services on the one hand, and poverty reduction on the other, while taking into account the global, regional, and local drivers of biodiversity loss in poor areas.

Tackling the root causes of both biodiversity loss and poverty can lead to complementary positive results. For example, reducing population pressure by promoting voluntary reductions in fertility in impoverished regions could support conservation of biodiversity and faster poverty alleviation (7). However, there

may be complex trade-offs, especially in the short term. Trade liberalization, for instance, might increase the supply of food commodities and could reduce prices in food-importing countries, which would remove some pressure on these countries' natural habitats. But reductions in trade barriers might also lead to increased production in food-exporting countries where commercial agriculture could increase vulnerability to deforestation, pests, diseases, and/or natural disasters, and might reduce the availability of ecosystem services (8, 9). Nevertheless, countervailing efforts to maintain biodiversity must be sensitive to human needs if they are to retain public support (10).

The scientific and development policy communities should focus on jointly articulating and addressing the critical research questions that, when answered, will help ensure that poverty alleviation and conservation efforts produce win-win outcomes, or at least minimize harm to either agenda. To ensure greater synergies, we suggest the following actions. Attention must focus on constructing and meeting a new biodiversity target for the remaining MDG period and beyond. The next target should be more specific, similarly time-limited, reasonably achievable, and should address the consequences of biodiversity loss globally and for the most vulnerable people and societies.

Any near-term gains in reducing extreme poverty will be maintained only if environmental sustainability is also achieved.

It should be supported by a small set of indicators (11) that measure trends in the state of biodiversity and ecosystem services, drivers of biodiversity loss and activities to safeguard biodiversity.

We need evidence-based interventions that can address both poverty reduction and environmental sustainability. In agriculture, for instance, we can use existing land more efficiently; we can pursue development that protects or enhances biodiversity; and we can improve productivity in ways that maintain ecosystem services, through institutional changes to secure better access to seeds, markets, and expertise, combined with adaptive applications of technologies (12). Similarly, finance and technology for adaptation, disaster management, and reduced emissions from deforestation and forest degradation (13) are particularly important in helping developing countries deal with climate change.

Future projects should explicitly monitor the impact poverty alleviation efforts have on ecosystems and their services; similarly, conservationists must better document the impact their interventions have on the poor. Ideally, interdisciplinary science that helps to identify the most cost-effective solutions will ensure that future environment and development projects are implemented, not just simultaneously, but in an integrated fashion.

Poverty alleviation and biodiversity agendas need to be jointly presented to policymakers. Establishment of a proposed Intergovernmental Platform on Biodiversity and Ecosystem Services to complement the existing Intergovernmental Panel on Climate

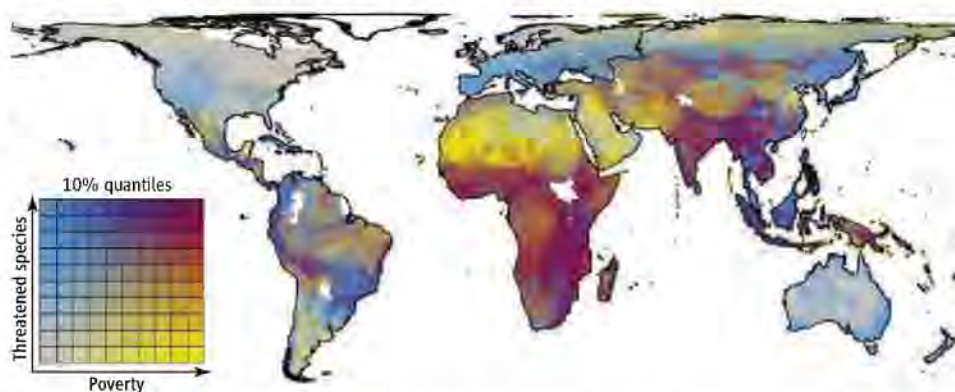


Fig. 1. Map of poverty and potential biodiversity loss, showing the level of poverty (proxied by the log rate of human infant mortality) combined with the log number of threatened species of mammals, birds, and amphibians per one-degree grid square (Behrmann equal-area projection). White areas represent missing data. Data from (14) and (15).

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Change may provide a means to enhance the quality and timeliness of the interactions between scientists and policy-makers at national scales and above. The GLOBE International Commission on Land Use Change and Ecosystems, made up of senior legislators from the G8+5 and several developing countries, provides another opportunity to bring policy-makers and scientists together. Similar initiatives will also be needed at the subnational scale.

The United Nations will convene a summit in 2010 to consider the second 5-year review of the MDGs and to catalyze action ahead of the 2015 MDG target year. We must

advise policy-makers and civil society organizations on the most critical initiatives needed to achieve the MDGs while preserving biodiversity and ecosystem services.

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ECOLOGY

Tracking Progress Toward the 2010 Biodiversity Target and Beyond

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In response to global declines in biodiversity, some 190 countries have pledged, under the Convention on Biological Diversity (CBD), to reduce the rate of biodiversity loss by 2010 (1, 2). Moreover, this target has recently been incorporated into the Millennium Development Goals in recognition of the impact of biodiversity loss on human well-being (3). Timely information on where and in what ways the target has or has not been met, as well as the likely direction of future trends, depends on a rigorous, relevant, and comprehensive suite of biodiversity indicators with which to track changes over time, to assess the impacts of policy and management responses, and to identify priorities for action. How far have we come in meeting these needs, and is it sufficient?

In 2006, the CBD adopted a framework of 22 cross-disciplinary headline indicators with which to measure progress toward the

target at a global level (4, 5). Countries are being encouraged to report progress at the national level using this framework, which is also being applied in regional initiatives such as “Streamlining European Biodiversity Indicators” (SEBI 2010). Other global multilateral environmental agreements, including the Ramsar Convention on Wetlands, the Convention on Migratory Species, and the Convention on International Trade in Endangered Species of Wild Fauna and Flora, are also adopting and adapting relevant subsets of the indicators.

However, with 2010 fast approaching, the indicator set is by no means complete. This is unsurprising given the short time since the framework was agreed upon. Of the 22 headline indicators, 5 are not being developed at a global scale, and there will be none to measure the status of access and benefit sharing, one of the three objectives

Biodiversity indicators used by policy-makers are underdeveloped and underinvested.

of the CBD. The remainder has been subdivided into 29 actual measures, of which only 9 can be considered well-developed, with established methodologies, reasonable global coverage (all continents except Antarctica, tropical and temperate regions, and developed and developing countries), and sufficient time-series data (at least three data points spanning at least 10 years) to demonstrate changes over time [(Table 1) and supporting online material (SOM)].

Even for these well-developed global indicators, there are challenges in terms of data availability, consistency, and relevance. Some indicators are only weak proxies for biodiversity, because the urgent need for indicators has often meant relying on existing measures designed for purposes other than tracking biodiversity change. For example, forest cover may be an acceptable proxy for timber stocks, but says less about the condition of forest biodiversity. Likewise, protected area coverage signals government commitments but does not in itself measure effectiveness in reducing biodiversity loss. These subtleties are beginning to be explored but require further effort.

Patchy data are another challenge, including gaps in data submissions for indicators compiled from national reports (6–9) and incomplete taxonomic and geographic coverage of indicators compiled directly from data. The most well developed direct measures of biodiversity are species indicators, such as the IUCN Red List Index (RLI) (10) and the Living Planet Index (LPI) (11). They are being used to inform and underpin a variety of other indica-

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tors (see SOM). Nevertheless, in the RLI, only a small number of taxonomic groups have been fully assessed, whereas, in the LPI, tropical species are poorly represented (12). Efforts are being made to improve representation in both of these indicators, including through a sampled RLI approach (13).

Information on genetic- or ecosystem-level changes in biodiversity is much patchier. Despite the promise of remote sensing and the increasing quality and availability of satellite imagery, translating this into meaningful metrics of change for freshwater systems, drylands, coastal and marine habitats, and other ecosystem types has proved challenging to date. Local and regional studies are available (14), but they are yet to be applied

globally. Likewise, indicators of genetic biodiversity are slowly being compiled for domesticated and cultivated varieties but not yet for wild relatives.

For the indicators that are under development, the race is now on to ensure adequate coverage and sufficient time-series data by 2010. Although progress has undoubtedly been made, for some, such as trends in genetic diversity and ecosystem fragmentation, a baseline and established methodology may be the most that can be expected. Some of these indicators require input from a range of disciplines not traditionally associated with biodiversity science, such as geophysics, economics, sociology, anthropology, agronomy, and health. The scientific community must be encouraged to engage in the development of these indicators and to provide case studies demonstrating how and why biodiversity losses have been reduced.

Whatever the indicators tell us, it is widely held that the target cannot and will not be achieved in its entirety (16). Although the current indicators will provide a partial story about both achievements and failures, there are gaps and missing linkages in the framework that mean it may not be sufficient to communicate the urgency of the message, to hold politicians to account, or to inform them of how best to act.

In October 2010, the Conference of the Parties (COP) to the CBD will review progress and agree on a new set of targets and a revised indicator framework. Whatever shape these targets take, the lessons for indicator development are clear. Indicators must be closely linked to the targets, but also to each other. We believe that a revised framework comprising a small set of headline indicators in four focal areas (pressures–threats, status–trends, benefits–services, and actions–responses) with underlying measures that are causally linked, will make it clearer to policy-makers how biodiversity loss affects people and how actions to reduce threats make a difference.

Continued investment must be made in the existing indicators to improve taxonomic, geographic, and temporal coverage, alongside support to develop measures at the finer (genetic) and broader (ecosystem) scales. Indicators of

the biodiversity impacts of a wider range of threats, including climate change, should be incorporated. Critically, indicators must be developed to fill a major gap regarding the effect of biodiversity change on the provision of ecosystem services. A balance must be found between developing too large and confusing an array of individual measures versus relying on a few aggregate indices that appear compelling but that mask complexity and can be misinterpreted. Quality-control efforts are needed to ensure that indicators are sufficiently scientifically rigorous, free of bias, and sensitive enough to detect meaningful change (16).

Indicators cannot be developed in the absence of reliable biodiversity data. Systematic global biodiversity monitoring (17, 18) would help, but this must be balanced with significant indicator capacity development at the national level. Better national indicators, developed as part of an inclusive international process, will enable better global syntheses beyond 2010. The scientific community must engage and encourage governments in this regard.

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Table 1. Current development of the headline biodiversity indicators within the CBD framework. ■ Fully developed with well-established methodologies and global time-series data, ■ under development, and ■ not being developed. Multiple labels indicate multiple measures under each headline. See also SOM and 2010 Biodiversity Indicators Partnership, www.twentyten.net.

CELL BIOLOGY

Expanding Functionality Within the Looking-Glass Universe

Steven R. Blanke

After she stepped through a looking glass into a mirror image of her own world, Lewis Carroll's adventures Alice soon recognized that the two worlds were perhaps not so similar after all. She intuitively felt that something about the very make-up of "looking-glass milk" was fundamentally different from that of the wholesome beverage she typically enjoyed (1). Indeed, nature has stocked our universe with biological substances that exist as two mirror image forms of one another. Nineteen of the 20 naturally occurring amino acids that make up proteins are "chiral," meaning that each can be arranged in two orientations around a central carbon atom. The result is a mixture of "mirror-image compounds" called L- and D-amino acids, which cannot be superimposed (see the figure), much in the way a person's left and right hands are not superimposable. One of the great mysteries of life has been the emergence of a strictly "left-handed" protein world where great attention has been paid to the L-amino acid building blocks (2–4), while D-amino acids are largely regarded as red-headed cousins who are easy to ignore. On page 1552 of this issue, Lam *et al.* challenge this perception, describing a role for D-amino acids in controlling bacterial responses to environmental cues (5).

Alice had good reason to be concerned, because while pairs of "mirror-image molecules" are identical in many respects (e.g., molecular mass, bond angles, and bond lengths), they often exhibit highly divergent biological properties, with potentially far-reaching ramifications (including exactly how Alice would manage to digest and metabolize milk proteins composed exclu-



Which universe? Additional functions for D-amino acids are being discovered in both bacterial and eukaryotic systems. This challenges the notion that D-amino acids are relatively unimportant in a universe dominated by left-handed (L-amino acid) proteins.

sively of D-amino acids). The apparent predominance of L-amino acids raises fundamental questions about the extent to which D-amino acids have major roles in biological systems. However, new functions for D-amino acids are now emerging, fueling new discussions. Adding to the debate, Lam *et al.* have determined that D-amino acids regulate cell wall remodeling in bacteria.

The cell wall provides the strength and rigidity needed for bacteria to withstand environmental stresses. It is constructed primarily of peptidoglycan, an elastic polymer consisting of sugars and amino acids arranged in a mesh-like lattice encasing the plasma membrane. One of the first biological roles identified for D-amino acids was the cross-linking of long peptidoglycan sugar chains by short peptides containing D-alanine and D-glutamate, which are thought to confer resistance to degradative enzymes that selectively hydrolyze linkages between L-amino acids.

For bacteria to thrive and survive, peptidoglycan must demonstrate a degree of plasticity. Bacterial cells that are dividing rapidly in nutrient-rich medium must allocate peptidoglycan to new daughter cells. In times of stress, peptidoglycan must be remodeled to function as the stress-bearing component of the bacterial cell wall. However, the fac-

Although once thought to be largely irrelevant in the biological world, new and unexpected functions for D-amino acids continue to emerge.

tors controlling cell wall remodeling as bacterial cells pass from a nutrient-rich to a nutrient-poor environment had been largely unidentified.

While studying a mutant form of *Vibrio cholerae*, the etiologic agent of the pandemic diarrheal disease cholera, Lam *et al.* noted that changes in bacterial morphology consistent with cell wall remodeling were associated with an accumulation of several amino acids in the spent bacterial growth medium.

Surprisingly, the D- rather than L-form of two particular amino acids, methionine and leucine,

were the most active agents in causing a decrease in peptidoglycan synthesis and alterations in peptide cross-linking. A direct role for D-methionine and D-leucine in the regulation of cell-wall remodeling was supported by discovery of a novel *V. cholerae* enzyme necessary for synthesis of these two D-amino acids. Interestingly, the D-forms of two different amino acids were most active in inducing peptidoglycan alterations in the Gram-positive *Bacillus subtilis*.

Exactly how D-amino acid-dependent cell wall remodeling occurs remains to be determined. However, the finding that D-amino acids other than the canonical peptidoglycan components D-alanine and D-glutamate can be incorporated into cross-linking peptides suggests a direct mechanism by which altering the composition of peptidoglycan modulates the strength and flexibility of this polymer within the cell wall. However, it is possible that D-amino acids may also regulate the function of periplasmic enzymes that synthesize and modify the peptidoglycan polymer.

The repertoire of biological roles for D-amino acids continues to expand, with notable examples of potential regulatory functions. Several *Bacillus* species regulate the development of spores into vegetative

cells by altering the relative concentrations of available D- and L-alanine, which, respectively, inhibits or induces germination initiation by modulating the function of germination receptors on the surface of spores (6). The outermost capsule layer of some *Bacillus* species, including *B. anthracis*, the etiologic agent of anthrax, comprises extensive polymers of D-glutamate, presumably providing resistance to degradative proteases (7). D-Amino acids are increasingly being identified in naturally occurring antibiotics, immunosuppressive drugs, and antitumor agents (8). Although once thought to be exclusively the domain of bacteria, roles for D-amino acids in eukaryotic physiology have emerged. Endogenous D-serine functions as a neurotransmitter in the mammalian brain (9).

D-Aspartic acid is found at high concentrations in some mammalian cells and organs, and modulates hormonal secretion in neuroendocrine tissues (10).

In retrospect, Alice's musings were probably no accident, as her creator, Lewis Carroll, also led an alternate (although not quite mirror-image) life as the Oxford mathematician Charles Dodgson. Dodgson may have been familiar with and influenced by the work of a contemporary, the great French chemist and microbiologist Louis Pasteur. Pasteur had already published his findings on the chiral properties of tartaric acid, a common component of several palette-pleasing delectables found on this side of the looking glass, including wines, and some fruits and plants. The continuing discovery of additional func-

tions for D-amino acids will continue to challenge the notion that D-amino acids have been largely irrelevant during the rise of the left-handed protein universe.

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ECOLOGY

Seeing the Big Picture on Microbe Distribution

David J. Patterson

Statements about the distribution of organisms can be made at all levels of phylogenetic scope and taxonomic resolution. The distributions of organisms on Earth reflect the interplay of dispersive trends with opportunity, obstruction, and extinction over time. If dispersal dominates, taxa tend to be widely distributed, and we rationalize presences and absences with greater reference to ecology. Where dispersal is constrained, taxa are more endemic, and we seek explanations by reference to history. For microbes, the idea that "everything is everywhere, but the environment selects," first mooted by Sprengel almost 200 years ago, still maintains support (1–5), but a recent review of molecular data suggested that it is simplistic or wrong (6). Two reports in this issue (7, 8) help to evaluate which concept best describes the distributions of marine microbes. In doing so, they raise broader issues about the nature of biological knowledge.

On page 1539, Cermeño and Falkowski (7) report distribution patterns of marine diatoms (see the figure) in space and time, based on analysis of the Deep Sea and Ocean drilling projects' Neptune database. They show that diatom communities from polar locations



Traveling far and wide. Studies of marine diatoms (such as those shown here) (7) and thermophilic bacteria (8) show that dispersal plays a powerful role in shaping microbial distributions.

resemble each other in a way that vertebrate communities do not. The same is true for more temperate communities that are geographically remote. The authors did not find biogeographical traces of historical climate change. Their conclusions are consistent with the dispersal-dominated model.

On page 1541, Hubert et al. (8) add interesting metrics to the picture. They find that microbial communities in the cold Arctic seabed included thermophilic bacteria that could not be metabolically active. The stocks of such bacteria were constantly being replenished, with 10,000 spores arriving from elsewhere on every square centimeter of the sediments every year. These results establish that dispersal is extremely powerful and can have a global impact.

The results bear on another recent insight into microbial diversity and abundance: the "rare biosphere" (9). Using high-throughput sequencing technologies, Sogin et al. discovered that there were massively more species of microbes out there than have previously been documented. The formal catalog of prokaryote species contains only about 6000 taxa, yet the team found evidence of orders of magnitude more taxa in individual samples. Most of these taxa are represented by only a few individuals. Two models can explain this distribution. One is that each habitat includes a massive number of microbial niches, and that samples draw on very complex, diverse, and active communities. Alternatively, only a small proportion of the species are metabolically active, and the remainder consists of

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metabolically dormant forms that made their way to each habitat through dispersal.

Both studies (7, 8) are consistent with the second model of the rare biosphere. We may thus expect cold-adapted organisms to arrive at hot ocean vents and the microbial gut biota of dugongs (marine herbivores in the Indo-Pacific) to be found in the coastal waters of Vladivostok. But how can we resolve the inconsistency of these demonstrations of the power of dispersal with the molecular evidence of endemism gathered by Hughes-Martiny *et al.* (6)? And why is there a discontinuity when microbes and larger organisms are compared?

The answer to the first question is probably straightforward. Taxa, like seashores or clouds, are not discrete objects. This is most dramatically illustrated by prokaryotes, where an entity is a mirage: a shimmering exchange of genetic materials (10). What we consider the objects to be depends on the perspective we take. Just as the objects are indefinite, so will much of their biology be indefinite, and our evidence and the stories we tell must be interpreted in an appropriate context. As with all organisms, the distributions of microbes are determined by both history and environment. Any distribution can be seen as more or less endemic depending on the perspective that is chosen. Such a contextualized under-

standing reveals that biology is less simple than we would like it to be.

To address the second question, we must keep in mind that the phenomena of biodiversity emerge from the interplay of serendipitous evolutionary processes and complex ecological interactions. Their time scales extend from microseconds to millennia, and their physical scales range from nanometers to thousands of kilometers. This gives biology a unique scientific character in which the narrative is as important as an explanatory tool as is reductionism (11). Yet, most efforts to find meaning within biology emphasize the examination of the particular, an approach not well suited to discovering large-scale phenomena or unusual emergent properties that are likely to be evident as discontinuities. For these areas, a more macroscopic approach (12) has value, as has already been argued in the biodiversity sciences (13).

How do we facilitate an approach that will improve on reductionism when it comes to picking up patterns and discontinuities? At least part of the answer lies in the tools used by the current authors (7, 8) and by Sogin *et al.* (9). All these tools—whether new molecular technologies or informatics tools—have remarkable scalability. The Encyclopedia of Life (14), with a taxonomically intelligent infrastructure that can be applied to all

organisms, further confirms that biology can change to include a macroscopic perspective that complements narrative, hypothesis, and experiment. Historically, sweeping statements attracted criticism because they degraded the precision and accuracy of the units of knowledge. In contrast, the new tools not only scale well but retain all details with full fidelity. That is a crucial step forward.

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PHYSICS

Itinerant Ferromagnetism with Ultracold Atoms

Wilhelm Zwerger

Ferromagnets, such as those made of iron or nickel, are called itinerant because the electrons whose spins aligned to create the magnetic state are extended and are the same as the ones responsible for conduction. Ferromagnetism was a mystery for classical physics, and its explanation in terms of spin, exchange interactions, and repulsions between identical particles was a triumph of early quantum mechanics. However, it proved difficult to apply these early models to real ferromagnets in a quantitative way, both because the simple models neglect important features relevant in real materials and because theoretical tools to properly treat the strong correlation problem have only recently been devel-

oped. Fortunately, the simple models studied in the early days of quantum mechanics can also be applied to fermions other than electrons. On page 1521 of this issue, Jo *et al.* (1) provide evidence for an analog of ferromagnetism in an ultracold gas of neutral lithium-6 atoms. When repulsive interactions between these freely moving particles are sufficiently strong, a transition to ferromagnetic ordering is seen.

Heisenberg recognized that exchange interactions between electrons residing in atomic orbitals that overlap spatially could favor a spin-aligned state. The repulsive energy decreases as more spins flip to the majority spin state. Bloch extended Heisenberg's idea (2) to delocalized electrons in what is now known as "itinerant exchange" (3–5). Bloch showed that the ground state

Cold lithium atoms undergoing strong repulsions can be driven into a state that is an analog of ferromagnetic ordering.

of a free electron gas favors full spin polarization at low densities (2). The ground state energy per particle depends on k_F , the Fermi wave vector of the gas with an equal number of particles in each spin state. In his model, the fully magnetized state appeared when $k_F a_0 < 0.35$, where a_0 is the Bohr radius. However, the few systems that exhibit such low densities are not ferromagnetic. In fact, precise Monte Carlo calculations suggest (6) that the transition to a ferromagnetic state appears at k_F values that are about one order of magnitude lower than the simple Hartree-Fock estimate that Bloch used.

A major conceptual step was taken by Stoner (7–9), who introduced an exchange field, similar to the molecular field that had been postulated by Weiss. Thus, rather than actually exchanging multiple electrons, the

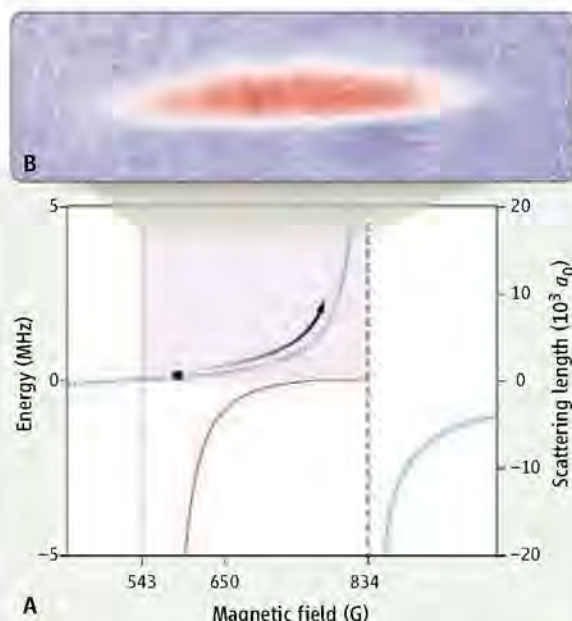
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physics could be viewed as the effect of a fluctuating spin environment on a single electron. The simplified model predicts itinerant ferromagnetism for sufficiently strong repulsion parameter U or for a high density of states at the Fermi energy. The simple Stoner model and its extensions have been used to describe ferromagnetism in the transition metals like nickel or iron. For quantitative predictions, however, a reliable theoretical determination of the effective U turns out to be very difficult.

The problem with applying the Stoner model is that, although magnets can be fairly simple samples experimentally, the electronic structure within them is incredibly complex. The theory can be applied more directly by examining a system that is physically difficult to realize—trapped ultracold atoms in a magnetic field—but that contains neutral fermions, for which the Stoner model of a zero-range repulsion between fermions of opposite spin is perfectly valid. The strategy of Jo *et al.* begins by trapping a gas of lithium-6 atoms in a 50:50 mixture of the two lowest hyperfine states, which are states that arise in the presence of a magnetic field. The population of these states is analogous to the spin states of the electron and is called pseudospin.

In contrast to electrons in solids, this pseudospin is conserved because the Pauli principle forbids transitions between the different hyperfine states (10). As a result, the total “magnetization” always vanishes; the signature of ferromagnetism is the formation of domains that contain only atoms in one of the hyperfine states.

The relative momenta of two ultracold atoms are so small that only s-wave, or “head-on” collisions occur between different hyperfine states. These collisions can be completely characterized by one parameter, the associated scattering length a (10, 11). The ground-state energy of the two-component ultracold Fermi gas derived with a mean-field approximation has a form similar to that derived by Bloch for electrons. However, the negative exchange contribution is replaced by a positive term that comes from the repulsion. When the system becomes a ferromagnet and has only one pseudospin component, this term completely vanishes at the expense of an increase of the kinetic energy. The competition between the kinetic energy that scales like k_F^2 and the repulsion proportional to $k_F^3 a$ favors a ferromagnetic configuration for $k_F a > \pi/2$, which now occurs at high densities.



Atomic models of ferromagnetism. (A) Repulsive interactions between ultracold lithium-6 atoms can result in an analog of ferromagnetism. The two lowest hyperfine states are analogs of spin and are called pseudospin states. Tuning of an applied magnetic field creates a Feshbach resonance that increases the repulsion between atoms (the colored region), which is reflected by an increase in their scattering length (shown in blue in units of the Bohr radius a_0). This broad resonance occurs at a magnetic field of 834 G; a narrower resonance occurs at 543 G. The arrow indicates the experimental ramp in magnetic field that begins at 590 G (indicated as a dot). Shown in red is the energy of the competing bound state on the repulsive side of the resonance where $a > 0$. (B) The absorption image shows one of the pseudospin states as the field is ramped up at a field of 812 G.

Driving cold atoms into the strong-repulsion regime is challenging. At the low densities typical for ultracold gases, Fermi wavelengths are almost 1 μm . To achieve scattering lengths of this size, Jo *et al.* use a Feshbach resonance in which the collision energy matches the energy of a closed-channel bound state (10, 11). The scattering length can be tuned simply by changing the magnetic field (see the blue curves in the figure, panel A).

One complication occurs when driving the atoms into the strong repulsive regime—this process competes with forming bound molecular states, whose energy is shown in red in the figure, panel A. This bound state can only be reached by three-body collisions, which normally would be rare but unfortunately occur at a high rate near the Feshbach resonance (12). In practice, therefore, the lifetime of ultracold gases with strong repulsive interactions is only on the order of milliseconds before molecule formation sets in.

What is the evidence, then, for Stoner-type ferromagnetism caused by strong repulsion in ultracold gases? Jo *et al.* ramped the magnetic field within a few milliseconds to values near the Feshbach resonance (see the figure). Beyond a critical final value, where $(k_F a)$

$\approx 1.9 \pm 0.2$, they observed three of the characteristic signatures expected for a ferromagnetic transition. Inelastic three-body collisions, which require fermions with opposite spin to be close together, were suppressed by domain formation. A minimum was seen in the kinetic energy of the atoms and then rose steeply because of an increase in k_F associated with the atoms forming local domains of the same spin state. In addition, a maximum was seen in the size of the atomic cloud again in qualitative agreement with the Stoner theory of a ferromagnetic transition, in which the ground-state pressure goes down because the fermions avoid the repulsive interaction.

Ideally, the expected ferromagnetic domains could be detected by phase-contrast imaging (10). The observed noise, however, was too large, and Jo *et al.* estimate that the domain size reached before molecule formation destroyed the ferromagnetic order was less than 2 μm , or only about 50 atoms in the same hyperfine state.

What are the perspectives opened by these intriguing results? Clearly, cold gases lack most of the complexities that still make ferromagnetism in real materials an open challenge in condensed matter physics. Yet, the

simplicity of cold gases, and in particular the tunability of interaction strengths, makes them an ideal tool to understand basic many-body problems that have remained open for decades. In particular, it is unknown beyond simple approximations like that of Stoner whether the strongly repulsive Fermi gas in the continuum has indeed a ferromagnetic ground state.

Cold atoms are thus a kind of quantum simulator that allows solving problems that are intractable otherwise. When cold atoms are also confined with optical lattices, magnetism would arise through superexchange induced by tunneling between nearest neighbor localized sites. Despite the small energy scales involved, superexchange has recently been realized with bosonic atoms (13). With fermionic atoms, this kind of system opens the way to investigate the predicted occurrence of ferromagnetism in the repulsive Hubbard model in three dimensions or, more generally, the competition between ferromagnetism and superconductivity near quantum phase transitions (14). Of particular interest is also the two-dimensional case where antiferromagnetism competes with d-wave superconductivity, a key issue in

models that are used to describe high-temperature superconductors.

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GEOPHYSICS

How River Beds Move

Philippe Frey¹ and Michael Church²

Insights into sediment transport at river beds can come from experiments in granular physics.

The transport of sediment through river channels has major consequences for public safety, management of water resources, and environmental sustainability. Most studies of sediment transport in rivers have focused on mass flux and its relation to water flow. Yet, after more than a century of work, there is no satisfactory theory for bedload, the component of the sediment load transported in contact with the stream bed. Bedload transport formulae often overpredict the actual rate by orders of magnitude (1). It is therefore difficult to predict, for example, the impact of disturbances such as extreme floods on the channel. Better insight may come from viewing bedload as a granular phenomenon.

Bedload transport can be divided into two stages (2): partial mobility of local bed surface material when part of the bed remains static but exposed grains may eventually move, and full mobility, when all grains move to a depth of several grain diameters. Grain-grain interactions over short time and length scales bear importantly on the predictability of both stages.

No single constitutive law reproduces the diversity of behaviors of cohesionless granular materials (3). Granular flows are often classified into three states: a gaseous state, in which flow is very rapid and dilute, and the particles interact by collision; an intermediate state, in which the material is dense but still flows like a liquid, the particles interact-

ing both by collision and friction; and a dense, quasistatic state, in which the deformations are very slow and the particles interact by frictional contacts. All three states might be found in free surface flows and in bedload.

Probably the most important phenomenon relevant to bedload is size segregation by shearing in free surface flows. Two distinct size segregation phenomena occur. When the coarsest fractions of the bed do not move and the smallest fractions are sufficiently fine, spontaneous percolation occurs. But when the bed is moving, kinematic sieving of the finer particles take place even if the size ratio is close to unity (4, 5). The usual result is a downward flux of smaller particles and an upward flux of larger particles, resulting in the segregation observed in river deposits (see the figure, panel A) and in a substantial reduction in transport.



Velocity and concentration profiles provide insight into the rheology of the granular flow. Regardless of grain sizes, interstitial fluid densities, and viscosities, the mean granular velocity profile has a similar shape, with a linear profile in the upper part and an exponential decay toward zero in the lower part (6). Velocity fluctuations permit computation of the granular "temperature" (the sum of streamwise and vertical variances of instantaneous velocity), a variable central to kinetic-theory modeling of low-density granular flows (7). In a study of size segregation (8), Hill and Zhang have shown that granular temperature profiles were particular to a size class, whereas mean velocity profiles were not.

Important differences between granular motion, as usually studied in both research and industrial contexts, and bedload transport in rivers include the very wide range of grain sizes and shapes normally present in fluvial sediments; the highly irregular geometry of river channels (itself a consequence of the movement and deposition of bed material); the highly variable forcing in rivers, both temporally and spatially; and the generally lower rates of flux. Nevertheless, important analogies may be exploited.

In rivers, full mobility is usually observed in sands, but also occurs in gravels under sufficiently strong flows. Few studies have addressed particle velocity and concentration profiles in full-mobility bedload (9, 10). The measured profiles have the same shape as their dry granular counterparts. Such results have been successfully compared with models of collisional grain flows based on kinetic theory or dense flow rheology (3, 11). As to segregation, bedload studies usually investigate the spontaneous percolation of fine grains into immobile gravels (12). In an experimental study, smaller beads have been introduced



Segregation through motion. (A) This vertical profile in a gravel river bar (in Vedder River, British Columbia, Canada) shows size sorting with an armored surface and finer material below. (B) In a quasi-two-dimensional experiment (13), kinematic sieving leads to the formation of layers of smaller transparent beads under larger moving black beads. This panel was redrawn from a video snapshot.

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into a bedload flow initially formed only of larger moving beads (13). After a while, a quasi-continuous layer of small particles developed beneath larger moving beads and above quasi-immobile larger beads (see the figure, panel B).

In the regime of partial mobility, processes are restricted to the surface of the bed, and all particles experience long periods of rest. This condition is characteristic of gravel transport. The propensity for grains of similar size to block each other leads to accumulations of similar-sized grains in restricted areas of the channel bed. Two phenomena command attention. Mobile materials collect in patches of similar size in the streambed, a phenomenon that mediates the overall sediment flux (14), while the largest stones in streambeds—usually only marginally mobile—congregate into clusters, chains, and cell-like arrangements that dramatically increase the overall stability of the bed (15).

The second case is particularly interesting from the granular perspective, because the stone structures represent a natural case of force chains that have been studied in the laboratory for more than a decade (16). In the extreme case of steep mountain channels containing relatively large stones, stone lines become channel-spanning force chains,

forming a distinctive step-and-pool morphology that maintains a stable channel in situations when any unconstrained stone would be swept away.

Heuristic models have been constructed for the development of surface structures, but the mechanisms that promote patch development and bed surface structures require additional experimental study before physically sound models may be developed. Stone lines and cells on the surface are relatively long-lived because, during most flows, their ultimate strength is not tested. This allows time for additional mechanisms to strengthen them further, beyond the state achieved by force chains in continuously deforming media. Hence, failure mechanisms are of particular interest. When extreme flows do break the stability of steep channels, life-threatening debris flows result.

Granular physics provides a good basis for improving our understanding of bedload transport at relatively high rates. However, surface phenomena that would simulate partial bedload transport remain essentially uninvestigated in granular physics. While imparting insight into the bedload problem, experiments on these phenomena would also open a new perspective in granular physics.

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PHYSICS

The Super of Superradiance

Marlan O. Scully^{1,2} and Anatoly A. Svidzinsky¹

In 1954, Robert Dicke introduced the concept of superradiance in describing the cooperative, spontaneous emission of photons from a collection of atoms. The concept of superradiance can be understood by picturing each atom as a tiny antenna emitting electromagnetic waves. Thermally excited atoms emit light randomly, and the emitted intensity is a function of the number of atoms, N . However, when the atomic “antennas” are coherently radiating in phase with each other, the net electromagnetic field is proportional to N , and therefore, the emitted intensity goes as N^2 . As a result, the atoms radiate their energy N times faster than for incoherent emission. It is this anomalous radiance that Dicke dubbed “superradiance” (1–3).

An even more interesting kind of radiation speedup can occur when a single photon is stored uniformly in a cloud of N atoms (see the figure, panel A). Suppose you have one atom that decays with a rate γ . Then suppose there are N such atoms close together in an atom cloud with only one of the atoms excited (but we don't know which one). Because there is only one atom excited, you might expect the decay rate to be γ . But if the atoms are symmetrically organized within the cloud, the decay rate is actually $N\gamma$ (1). This enhanced single-photon emission rate is “the greatest radiation anomaly” inherent in superradiance. Single-photon superradiance has become a subject of current interest (4–12), and promises to yield new tools for storing quantum information and deeper insight into the physics of virtual processes.

Dicke's point is that the N atoms act like one big atom and decay collectively. This is intuitive when the atoms are close together

Cooperative single-photon emission from an atom ensemble will provide insights into quantum electrodynamics and applications in quantum communication.

compared to the wavelength of radiation λ . When the same symmetric state is formed but the atomic cloud size is larger than λ , there is no longer constructive cooperation in radiation emission. The atoms will trap the light, decreasing the emission rate.

Nevertheless, it is possible to produce a state such that the large cloud also emits radiation with an enhanced rate proportional to $N\gamma$ (4, 5). This is important because in quantum optics the sample is usually large compared to λ .

However, things are a bit trickier here. More subtle and interesting physics come into play, extending from quantum information and a new kind of cavity quantum electrodynamics (QED) (13), to new insights into quantum field theory (9–12).

The essential new physics is the transition from the coherent antenna array to the single-photon state in which cooperative emission is due to N entangled atoms (not N coherent

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emitters). This is made possible by conditioned preparation of the initial atomic states (see the figure, panel A) (4, 5).

With the large sample, however, it is not so clear why the emitted photon should go in the same direction as the exciting photon given that there is no antenna dipole associated with the atoms (see the figure, panel B). One atom is excited, but we do not know which one. The answer is associated with timing: The atoms at the front of the sample are excited first and those at the back, last (4, 5). These excitations appear as spatial phase fac-

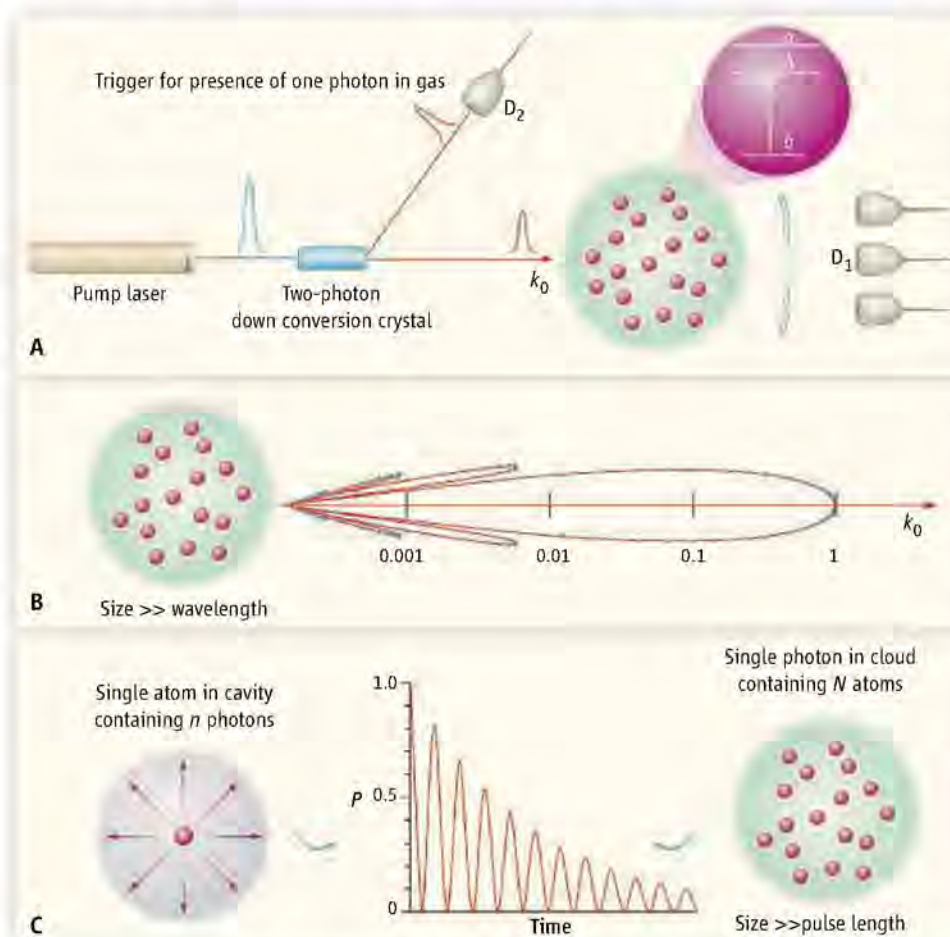
tors. It is this timing that yields directionality in the emitted radiation. Without the timed excitation, the radiation will be substantially trapped in the gas (11).

In particular, in the conditioned excitation case, the decay rate continues to be proportional to the number of atoms; but it also involves the diffraction factor $(\lambda/R)^2$, where R is the radius of the sample. This is the case for gas clouds that are large compared with λ but small compared with the size of the radiation pulse length L_p . However, when $R > L_p$, the coupled atom-radiation system

shows absorption-emission oscillations (see the figure, panel C) that are similar to those observed in cavity QED (13), where the Rabi oscillation frequency is determined by the volume of the cavity and the number of photons in the cavity. In the present case, the oscillation frequency is determined by the volume of the cloud and the number of atoms (14). This surprising result is indeed a new kind of cavity QED.

Another fascinating aspect of single-photon superradiance is the collective N -atom Lamb shift, which is due to the rapid emission and reabsorption of (virtual) photons (10–12). As the decay rate is enhanced by collective emission, so too is the frequency shift associated with the virtual photons. Furthermore, the virtual photons dramatically change the evolution of trapped states (11). They provide new decay channels, which ultimately result in a slow decay of the otherwise trapped state. However, for the rapidly decaying states, these virtual processes are relatively unimportant (11). In such a case, virtual photons excite other states with only a relatively small probability, depending on the size of the atomic cloud. In addition, the essentially new many-particle Lamb shift is not divergent. That is, the usual single-atom Lamb shift calculations involve infinities, high-frequency cutoffs, and so forth. However, in the many-atom version, the most interesting physics comes from this “infinity-free QED.”

A single photon stored in a large cloud of atoms provides new insights into the radiation physics of single-photon superradiance, virtual photons, and more. The single-photon states also have potential for application to quantum informatics.



Collective action. (A) Conditioned excitation prepares the timed uniform state in three logical steps (4): (i) Consider a pair of short single-photon pulses produced by a down converter (which absorbs one “blue” photon and emits two lower-energy “red” photons). A count in detector D_2 ensures that a photon of wave vector $\sim k_0$ is entering the atomic cloud at some time t_0 . (ii) The atoms are detuned from resonance by an amount Δ so that the excitation probability is weak and every atom is equally likely to be excited but at different times, depending on its position. (iii) Most of the time the photon will pass through the gas, and a count is registered in the “perfect” detector D_1 ; lack of a count tells us one atom is excited, but we don’t know which one. Then, conditioned on a count in D_2 , but not in D_1 , the detuning Δ is switched to zero. The atoms are now resonant with k_0 and emit spontaneously. (B) For a large atomic sample, the conditioned preparation depicted in (A) results in a radiation pattern that is strongly peaked in the k_0 direction. To a good approximation, the timed excitation yields emission speedup, which is proportional to the number of atoms and the solid diffraction angle given by the squared ratio of the wavelength to the sample size. Evolution of the single-photon timed state in the large sample has much in common with evolution of the symmetric state for a small atomic cloud. (C) For a very large cloud, the photon is reabsorbed and reemitted many times and the atomic state oscillates with a frequency that goes as $\sqrt{N}$. This is to be compared to the cavity QED scenario (13) in which an atom is cycled between the ground and excited states with a frequency which goes as $\sqrt{n}$, where n is the number of photons in the cavity. P is the probability that the atom is excited.

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Macroevolution of Complex Retroviruses

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Retroviruses are unusual among microorganisms in leaving a "fossil record" in the form of endogenous viral insertions within their hosts' genomes. However, insertions before the radiation of mammalian orders lack both retroviral accessory genes and contemporary infectious relatives (1) and thus provide limited insight into the coevolution of complex retroviruses and mammalian innate antiviral responses (2). We have found that foamy viruses, complex retroviruses currently infecting many mammals, are present within the genomes of sloths. By combining phylogenetic, genomic, and biogeographic methods, we have established that foamy viruses circulated among ancestral mammals >100 million years ago (Ma), demonstrating the survival of an infectious lineage of complex retroviruses across an entire geological era.

We screened all available mammalian genomes and identified foamy virus insertions only in the two-toed sloth, *Choloepus hoffmanni*, which belongs to the basal mammalian group Xenarthra. These sequences, termed SloEFV (sloth endogenous foamy virus), group robustly with contemporary infectious foamy viruses in phylogenies (3). We constructed a consensus ~11.5-kb SloEFV genome that could be aligned with contemporary strains and that exhibited typical foamy virus characteristics, including sequences similar to the accessory genes *tas* and *bet* (3).

Genomic analysis points to an ancient SloEFV origin. *C. hoffmanni*'s genome contains hundreds of SloEFV elements, most of which have lost their coding regions through recombination. Only 72 elements contained >1 kb of coding region, all of which carried numerous stop codons, frame shifts, insertions, and deletions. We used two independent approaches to determine the age of the SloEFV germline invasion. First, we measured genetic distances among eight elements that were identified as having arisen via host genome duplication events. By applying a xenarthran-specific rate of neutral evolution (3), we obtained a minimal SloEFV age of 39 million years (range from 34 to 45 million years; minimal because the earliest duplication event must postdate SloEFV germline invasion). Second, we determined the taxonomic

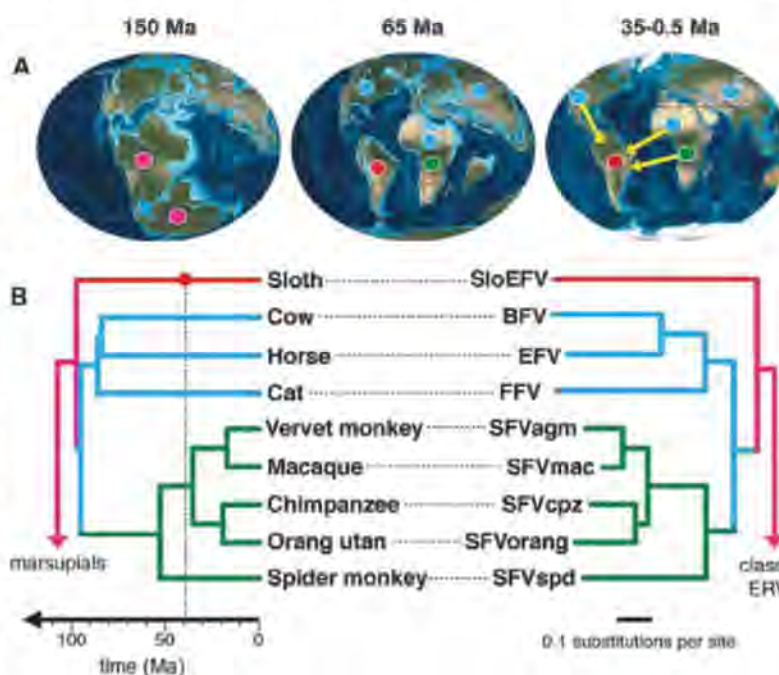


Fig. 1. (A) Estimated positions of Cenozoic landmasses and mammalian lineages. At 150 Ma, Old and New World landmasses were connected, and ancestral eutherian mammals (pink) existed within this range. From ~100 to ~30 Ma, xenarthrans (red) were geographically isolated from primates (green) and other boreoeutherian mammals (blue). SloEFV invasion of the sloth genome (>39 Ma, range from 34 to 45 Ma) thus occurred before the arrival of boreoeutherians in South America. **(B)** Foamy virus phylogeny (right; scale bar indicates amino acid changes per site) is congruent with that of mammals (left; scale bar, Ma) (5). Red circle denotes 39 Ma, our estimate of the latest possible date of SloEFV genome invasion.

distribution of SloEFV by polymerase chain reaction screening of tissue samples from five further xenarthran species: Insertions were detected in two- and three-toed sloths but were absent from anteaters and armadillos. SloEFV sequences from four sloth species did not cluster phylogenetically; indeed, we observe phylogenetically robust grouping of elements from different species (3), conservatively indicating that SloEFV entered the xenarthran germline before the divergence of two- and three-toed sloths (~21 Ma) but after the anteater-sloth split (~55 Ma) (4). Before this, foamy viruses circulated in xenarthran ancestors in an exogenous form.

These minimum ages are highly important in the context of mammalian biogeography: Xenarthrans diverged from other mammals ~105 Ma (5) and were isolated in South America as landmasses separated throughout the early Cenozoic (Fig. 1A). Mammals such as primates and rodents that evolved outside South America likely arrived there after 30 Ma (6), precluding them from having introduced SloEFV to xenarthrans upon their arrival. Phylogenetic comparison of foamy viruses and their hosts strongly supports a coevolutionary history tracing back to the origin of mammals: Topologies of virus

and host phylogenies exactly match (Fig. 1B), and viral branch lengths are significantly correlated with mammalian divergence times [$R^2 = 0.74$; $P < 0.0001$, robust to the exclusion of the sloth branch and of primates (7)]. See (3) for details.

The descendants of foamy viruses that infected ancestral mammals during the Cretaceous thus diverged in concert with their hosts throughout the Cenozoic and have persisted in a surprisingly unchanged form until today, supporting the idea that evolutionary constraint can maintain viral genomic conservation over many millions of years despite exceptionally high short-term rates of mutation (8). Furthermore, SloEFV's identification indicates that retrovirus accessory genes and mammalian mechanisms of innate immunity will be best understood when considered as the joint products of macroevolutionary conflict played out over a geological time scale.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/325/5947/1512/DC1
Materials and Methods

Figs. S1 to S4

Table S1

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Gold Helix Photonic Metamaterial as Broadband Circular Polarizer

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We investigated propagation of light through a uniaxial photonic metamaterial composed of three-dimensional gold helices arranged on a two-dimensional square lattice. These nanostructures are fabricated via an approach based on direct laser writing into a positive-tone photoresist followed by electrochemical deposition of gold. For propagation of light along the helix axis, the structure blocks the circular polarization with the same handedness as the helices, whereas it transmits the other, for a frequency range exceeding one octave. The structure is scalable to other frequency ranges and can be used as a compact broadband circular polarizer.

Metamaterial research has largely been stimulated by proposals and demonstrations of negative phase velocities (1–3), “perfect lenses” (4), or invisibility cloaking (5–7). Strong chirality has brought yet another new twist to this emerging field (8–13). Chirality is inherently a three-dimensional (3D) phenomenon and occurs, for example, for DNA, cholesteric liquid crystals, screws, and circular metal helices (14). Chiral optical materials mix electrical and magnetic responses such that magnetic dipoles are excited by the electric component of the light field and vice versa. For pure chirality, the locally induced magnetic (electric) dipoles need to be parallel to the local exciting electric (magnetic) field. In this case, the eigenpolarizations correspond to circular polarization of light, whereas they are elliptic in the more general non-parallel (i.e., bianisotropic) case (15, 16). For example, chiral metallic metamaterial structures have led to giant gyrotropy (9), circular dichroism (10), and negative phase velocities (8) at microwave (11) and far-infrared frequencies (12). However, all these phenomena have been restricted to narrow frequency ranges, which is a major drawback for many potential applications.

In metamaterials, the narrow frequency response originates from the internal resonances of the individual building blocks. In ideal effective media, the interaction among these building blocks is negligible. The situation is reversed in, for example, cholesteric liquid crystals where the building block (the motif) exhibits only a negligible resonance. There, the interaction among the periodically arranged unit cells is crucial. It leads to Bragg resonances that are again fairly

narrow. In our work on gold-helix structures, we combine internal and Bragg resonances leading to a broadband response. Strictly speaking, these metamaterial structures lie in between photonic crystals and effective media; hence, we refrained

from retrieving effective material parameters in this work [in contrast to recent theoretical work (17)].

The geometry and the anticipated optical response are illustrated in Fig. 1 [for computational details, see (18)]. We start with a usual split-ring resonator (SRR) (Fig. 1A), a ring with a slit that can be viewed as a tiny resonant electromagnet (19–21) into which the incident light field induces a circulating and oscillating electric current, giving rise to a local magnetic field (magnetic dipole). Adiabatically pulling one end of this planar SRR out of the plane leads to one pitch of a circular helix (Fig. 1B). Thus, the electromagnetic modes of SRRs and helices with one pitch are closely related. Intuitively, a helix under normal incidence of light acts somewhat similarly to an SRR under oblique incidence with respect to the direction normal to the SRR plane. However, extrinsic chirality (22, 23) observed for planar arrays of SRRs excited under oblique incidence (24) also leads to additional linear birefringence (22, 24). Hence, in general, the polarization eigenstates do not correspond to circular

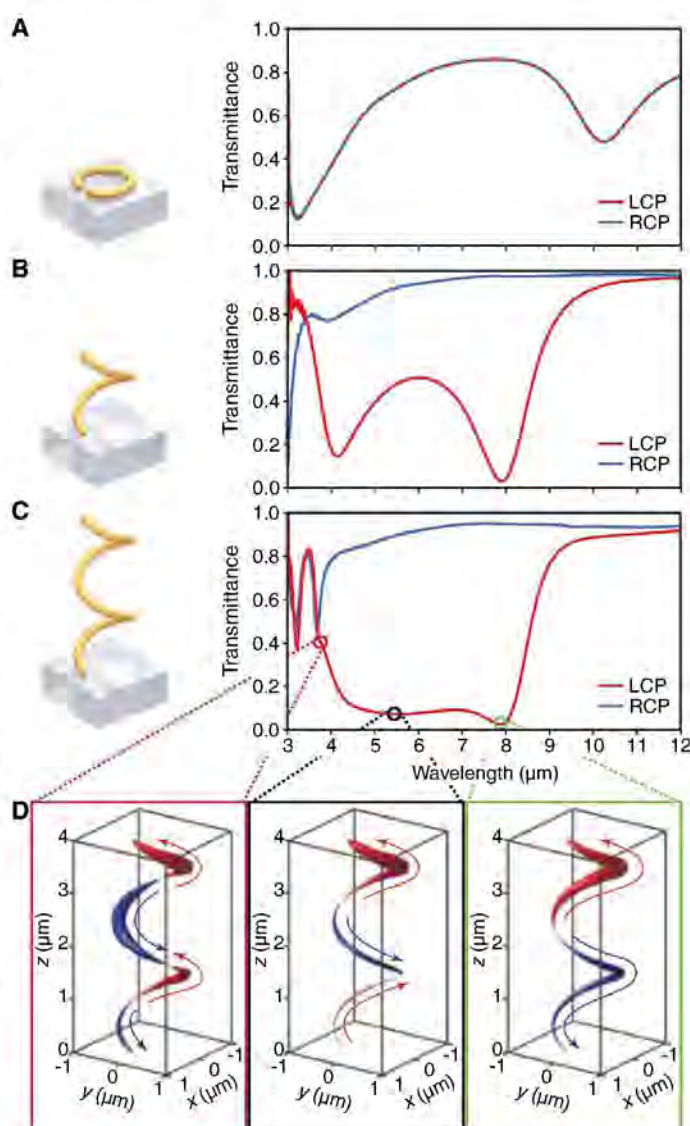


Fig. 1. Connection between split-ring resonators (SRRs) and metal helices. The 2 by 2 μm unit cells with 2 μm helix pitch used in the calculations in (A) to (C) are shown in the left column, normal incidence transmittance spectra for light impinging from the air side (no analyzer behind sample) in the right column. RCP and LCP refer to right and left-handed circular polarization of the incident light, respectively. (A) Planar SRR. Here, the RCP and LCP spectra are indistinguishable. (B) Adiabatically pulling the metal wire of an SRR out of the substrate plane leads to one pitch of a (left-handed) metal helix. (C) Two helix pitches (left-handed). (D) Snapshots of the electric current distribution along the metal wire for the three wavelengths [open dots in (C)]. The absolute value of the current is encoded by the curve thickness, the sign by red and blue (see arrows).

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but rather to elliptic polarization in that case. Linear birefringence is largely eliminated in our 3D helix design. Indeed, for the conditions of Fig. 1B, intensity conversion of the incident right-handed circular polarization (RCP) with high transmittance is below 5% in the 3.75 to 7.5 μm range.

The situation gets more complex for the case of two helix pitches (Fig. 1C). Intensity conversion of incident circular polarization is again low (below 5% in the same sense as above). However, we find a transition from sharp resonances for one helix pitch and left-handed circular polarization (LCP) in Fig. 1B to a broad stop band for two pitches in Fig. 1C (LCP). To clarify the nature of this broad stop band, we depict snapshots of the current distribution for three selected characteristic wavelengths (Fig. 1D). The three depicted modes closely resemble standing waves; that is, the positions of their current nodes change only slightly with time. The number of nodes decreases from three to one as wavelength increases for the three modes. The superposition of these three modes leads to the broad spectral response. This behavior is somewhat analogous to that for coupled SRRs (16), where magnetization waves (25) can form bands out of previously sharp individual resonances. In other words, in addition to the internal resonances, the Bragg resonance becomes important as well. The calculations are rather similar if we treat the metal as an ideal conductor rather than as a Drude free-electron metal with finite plasma frequency and damping. This observation indicates that the effects can, in principle, be scaled by structure size to any desired wavelength range, provided that the operation wavelength is sufficiently below the metal plasma frequency. This observation also indicates that, in an ideal structure, the missing light for the low-transmittance circular polarization is reflected rather than absorbed.

Our fabrication of corresponding structures for mid-infrared frequencies is outlined in Fig. 2. The idea is to infill a polymer template by electrochemical deposition of a metal [for experimental details, see (18)]. We chose gold because of its excellent optical properties at mid-infrared wavelengths and because, unlike silver, it does not deteriorate with time. Helix-shape air voids in the polymer structure are required for this purpose. Most previous work on direct laser writing (DLW) of 3D polymer structures has used negative-tone photoresists (26); the work reported in (27) is a notable exception. For negative-tone photoresists, only the sufficiently exposed regions remain after the development process. However, because of the proximity effect, fabrication of narrow pores in a bulk matrix is rather difficult in this case. Thus, we used a positive-tone resist for which only those regions that are sufficiently exposed by light are removed in the development process. Figure 3 shows corresponding structures made by using a commercially available 3D DLW system. To allow for electrochemical dep-

osition, a 25-nm thin optically transparent film of indium-tin oxide (ITO) is evaporated as the cathode onto a glass substrate before the photoresist is spun on. Typically, we use a photoresist thickness of 10 μm . After development, the structure is placed into an electrochemical cell, where a voltage is applied between the ITO film (at one side of the glass substrate) and the anode, which is immersed in the electrolyte. A constant current source controls the electrical current and, hence, the growth rate. After gold infiltration up to a certain level determined by the current density

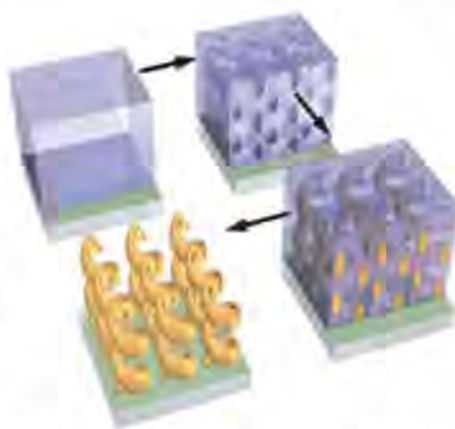
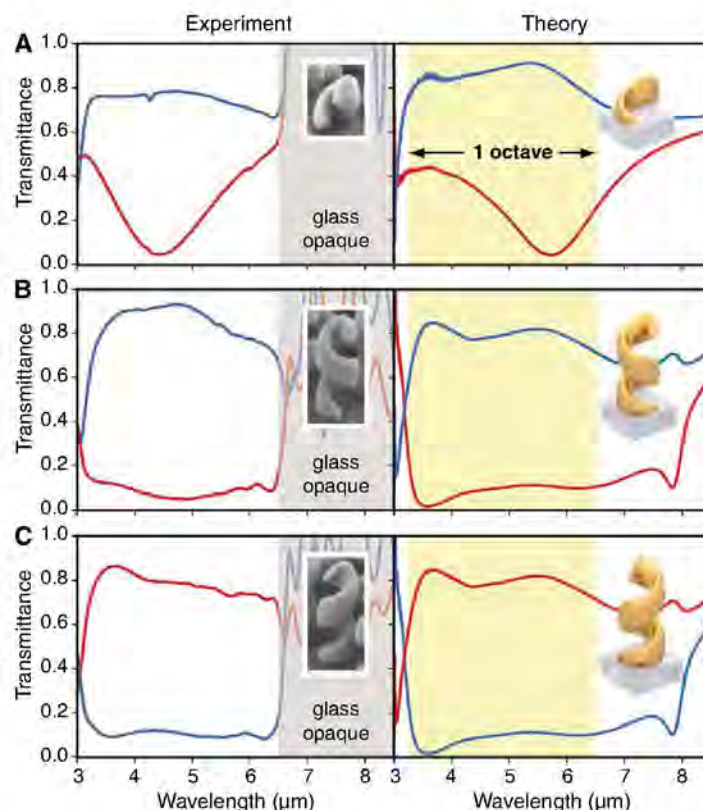


Fig. 2. A positive-tone photoresist (blue) is spun onto a glass substrate covered with a 25-nm thin film of conductive indium-tin oxide (ITO) shown in green. After 3D DLW and development, an array of air helices in a block of polymer results. After plating with gold in an electrolyte, the polymer is removed by plasma etching, leading to a square array of free-standing 3D gold helices.

Fig. 4. Normal-incidence measured and calculated transmittance spectra (no analyzer behind sample) are shown in the left and right columns. LCP and RCP are depicted in red and blue, respectively. (A) Slightly less than one pitch of left-handed helices, (B) two pitches of left-handed helices, and (C) two pitches of right-handed helices (see insets). For wavelengths longer than 6.5 μm , the glass substrate in the experiments becomes totally opaque. Hence, transmittance cannot be measured. For wavelengths below 3 μm , light can be diffracted into the glass substrate ($a = 2 \mu\text{m}$ and refractive index $n = 1.5$), giving rise to Wood anomalies.



and the growth time, we completely remove the polymer by exposing the composite structure to air plasma. Oblique-view electron micrographs of the gold structures fabricated (Fig. 3B) show that these structures have a fairly small gold sur-

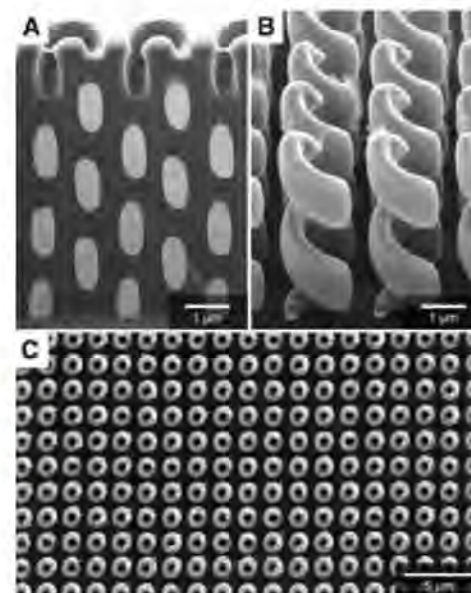


Fig. 3. (A) Focused-ion-beam (FIB) cut of a polymer structure partially filled with gold by electroplating (compare lower right part of Fig. 2). (B) Oblique view of a left-handed helix structure after removal of the polymer by plasma etching. (C) Top-view image revealing the circular cross section of the helices and the homogeneity on a larger scale. The lattice constant of the square lattice is $a = 2 \mu\text{m}$.

face roughness and come close to the ones theoretically anticipated in Fig. 1. Their footprint is 40 by 40 μm .

Figure 4 compares measured and calculated optical transmittance spectra for circular polarization of the incoming light propagating along the helix axis. Broadband optical spectroscopy in the few- μm wavelength range using incident circular polarization of light is not standard at all. Thus, by introducing the combination of a linear polarizer and a mid-infrared super-achromatic quarter-wave plate, we have specifically modified a commercial Fourier-transform spectrometer combined with a microscope for that purpose (18). The measured spectra in Fig. 4 reveal the theoretically anticipated blocking of one of the two circular polarizations, whereas the other circular polarization is transmitted. A large transmittance ratio results in the wavelength range from 3.5 to 7.5 μm , which exceeds one octave. Some engineering of the helix parameters would allow for further improvement of the suppression ratio. For conical helices with a diameter that continuously increases along the helix axis—rather than for the constant helix diameter discussed here—antenna theory (28, 29) promises bandwidths considerably exceeding one octave. This approach could lead to a further increase of the circular-polarizer operation bandwidth.

Metallic wire-grid linear polarizers (“one-dimensional metamaterials”) have been known since the pioneering experiments on electromag-

netic waves by Heinrich Hertz in 1887. Nowadays, they are still widely used for broadband applications. Because of the obvious wavelength dependence of quarter-wave plates, broadband conversion of linear into circular polarization is nontrivial in many frequency ranges. Our 3D metamaterial based on metal helices can be viewed as the circular analog of Hertz’s device.

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Control of Spin Precession in a Spin-Injected Field Effect Transistor

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Spintronics increases the functionality of information processing while seeking to overcome some of the limitations of conventional electronics. The spin-injected field effect transistor, a lateral semiconducting channel with two ferromagnetic electrodes, lies at the foundation of spintronics research. We demonstrated a spin-injected field effect transistor in a high-mobility InAs heterostructure with empirically calibrated electrical injection and detection of ballistic spin-polarized electrons. We observed and fit to theory an oscillatory channel conductance as a function of monotonically increasing gate voltage.

Many types of spintronic devices have been proposed, investigated, and developed. However, the spin-injected field effect transistor (spin FET), which lies at the heart of spintronics, has yet to be realized.

Proposed by Datta and Das (1), the demonstration of a spin FET involves spin injection and detection using a ferromagnetic source and drain. However, a special feature of the spin FET is the periodic modulation of source-drain conductance as controlled by gate voltage—induced precession of the injected spins. Electrical spin injection and detection have been demonstrated in a variety of semiconductors (2–6). Carrier spin precession has been induced by using an external magnetic field and detecting the Hanle effect, a Lorentzian-shaped magnetoresistance caused by precessional dephasing of diffusing spins, in

materials with relatively small spin-orbit interaction such as GaAs and Si (3–5). However, modulating the channel conductance by using an electric field to induce spin precession has remained elusive. A material with large spin-orbit interaction will not permit the observation of the Hanle effect, yet this type of material is necessary for gate voltage-induced spin precession. These two phenomena are mutually exclusive within any single material. We used a high-mobility InAs heterostructure with strong intrinsic spin-orbit interaction α , and we measured the nonlocal channel conductance (5, 6) rather than the direct source-drain conductance suggested by Datta and Das. Conventional lateral spin valve techniques measured the population of ballistic spins. Shubnikov–de Haas (SdH) experiments provided an independent measurement of the dependence of the spin-orbit interaction on gate voltage. Apart from a small phase shift, the oscillatory conductance that we measured fits to theory (1) with no adjustable parameters. The temperature dependence indicates that the modulation is only observed when the injected electrons have ballistic trajectories to the detector.

A conventional lateral spin valve device (Fig. 1A) is a convenient structure to investigate spin injection and detection for several reasons. First, the ferromagnetic (FM) electrodes have a uniaxial shape anisotropy that can create binary

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magnetization states along the y axis, $\pm M_y$. A small external magnetic field applied along the y axis (B_y) can create conditions with the injector (source) and detector (drain) magnetizations parallel or antiparallel, resulting in relatively high or low spin-dependent voltages at the detector (2, 7, 8). Second, a small channel length, L , between injector and detector can be defined lithographically. Third, in the “nonlocal” configuration (5–12), the bias current is grounded at one end of the sample, there is no charge current in the vicinity of the spin detector, background effects are minimized, and the signal-to-noise ratio is maximized. Spin-polarized carriers with ballistic trajectories along the $+x$ and $-x$ directions are injected with equal probability.

In a two-dimensional electron gas (2DEG) channel with strong spin-orbit interaction, the structural asymmetry provides an intrinsic electric field along the z axis, $E_{z,0}$, where the subscripts denote the z direction and zero gate voltage. In the rest frame of a carrier moving with a weakly relativistic Fermi velocity, $v_{Fe} \sim c/300$, with c the speed of light, electric field $E_{z,0}$ transforms as an effective magnetic field $B_{Ry,0}$, which is called the Rashba field (13). The Rashba field is perpendicular to the directions of the carrier velocity and the electric field. In Fig. 1, $B_{Ry,0}$ is along the y axis and has no effect on carriers that are injected with spin polarization also along the y axis (Fig. 1A). Datta and Das predicted, however, that carriers injected with spin polarization along the x axis would precess under the influence of $B_{Ry,0}$, a condition that occurs when the magnetization of the injector is oriented along the x axis (Fig. 1B). The magnitude of E_z can be modulated by a variable gate voltage V_G ; the magnitude of the Rashba field changes, B_{Ry} is proportional to E_z , and the precession rate therefore changes as a function of V_G . When the detector is also a FM electrode with magnetization along the x axis and carriers have ballistic trajectories from injector to detector, the channel conductance of the structure in Fig. 1B is predicted to oscillate periodically as a function of monotonically increasing gate voltage, because the detector voltage will be high when a detected spin has its orientation parallel with that of the detector and the detector voltage will be low when the spin is antiparallel (I). This is a relativistic electric field analog of Larmor waves (14). Whereas Larmor waves may be detected in superposition with a diffusive resonance feature, the spin-orbit interaction in a spin FET is so large that spin orientation is randomized after only a few scattering events, and the diffusive analog (the Hanle effect) is not observed [supporting online material (SOM) text S1].

Our devices consist of two $\text{Ni}_{81}\text{Fe}_{19}$ electrodes on top of an InAs high-electron mobility transistor (HEMT) channel and a gate electrode (15). The InAs HEMT (6, 16) was grown by molecular beam epitaxy on a semi-insulating InP (100) substrate. The single quantum well, which functions as a 2DEG channel, has a depth of

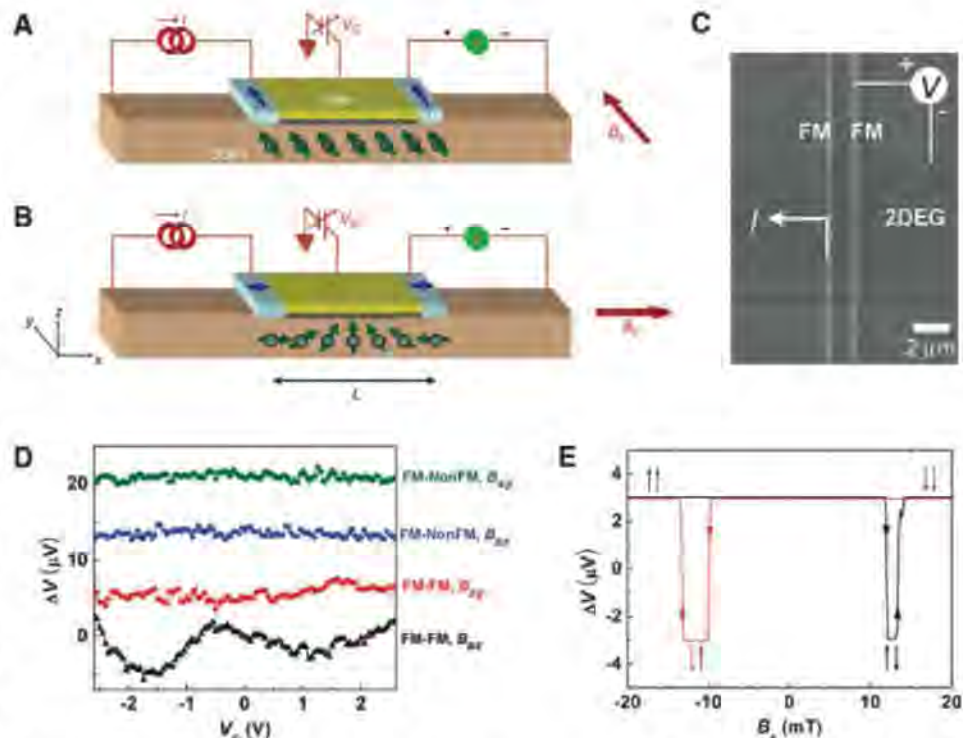


Fig. 1. Lateral gated spin valve device with an external magnetic field ($B_a = 0.5$ T) applied along the y axis (A) and x axis (B). In (A), the magnetizations of the FM electrodes are shown oriented along the y axis. The injected spin-polarized electrons are oriented along the y axis and do not precess under the influence of the Rashba field B_{Ry} . (B) shows the electrons injected with spin orientation along the x axis, perpendicular to B_{Ry} , and they precess under the influence of the effective field. (C) Scanning electron micrograph of the device. For clarity, the image was taken before depositing the gate oxide and electrode. (D) Observation of oscillatory conductance from injector to detector with $T = 1.8$ K. Gate-controlled spin precession occurs in configuration (B) (black trace) and not in configuration (A) (red trace). The green and blue traces represent data from a control sample that has a ferromagnetic injector but a nonmagnetic detector. The channel length is $L = 1.65$ μm and the bias current is $I = 1$ mA. The plots are shifted for clarity. (E) Conventional, nonlocal, lateral spin valve magnetoresistance measurement using configuration (A) at $T = 1.8$ K. The black and red lines correspond to field sweep-up and -down, respectively. The pairs of arrows indicate the magnetization alignments of the two FM electrodes, either parallel or antiparallel.

35.5 nm from the top surface. The carrier density and mobility of the 2DEG are $n_s = 1.8 \times 10^{12}$ to 2.8×10^{12} cm^{-2} and $\mu = 50,000$ to $60,000$ $\text{cm}^2 \text{V}^{-1} \text{s}^{-1}$ at temperature $T = 1.8$ K, respectively. The channel, defined by a mesa etch, is oriented with x along the $\langle 110 \rangle$ direction and has a width $w = 8$ μm . The two FM electrodes were fabricated with electron beam lithography and lift-off and have lateral dimensions of 0.4×80 μm and 0.5×40 μm (Fig. 1C). Samples were made with FM electrode spacings of $L = 1.25$ and 1.65 μm , measured center to center.

An example of the oscillatory conductance modulation is shown in Fig. 1D. An external magnetic field, $B_a = 0.5$ T, was applied to fix the magnetization orientations of the FM electrodes in a chosen direction, thereby determining the axis of spin injection and detection. The nonlocal channel conductance was measured as a function of gate voltage for the range $-3 \leq V_G \leq 3$ V. The red trace presents data for field B_{ay} applied along the y axis (Fig. 1A). The orientation of injected spins along the y axis is parallel to the Rashba field. There was no spin preces-

sion and no modulation of voltage recorded by the detector. For the data represented by the black trace, the external field $B_{ax} = 0.5$ T was large enough to overcome the shape anisotropy of the FM electrodes. The magnetization orientations of injector and detector are along the $+x$ direction (Fig. 1B), and the injected spin orientation is perpendicular to the Rashba field. The spin precession varies as a function of gate voltage, and an oscillation of detected voltage as a function of V_G was observed. The range of gate voltage is sufficiently large that more than one full cycle of voltage oscillation was recorded.

Control experiments were performed to further confirm that the voltage oscillation originated from the detection of spin precession in the channel. The devices used as controls were made with the same geometry and lithographic processing but with the FM detector replaced by a nonmagnetic electrode composed of an In (50 nm)/Au (30 nm) film. Identical transport measurements were made, but no voltage modulation was observed, regardless of the direction of the external field (blue and green traces in Fig. 1D).

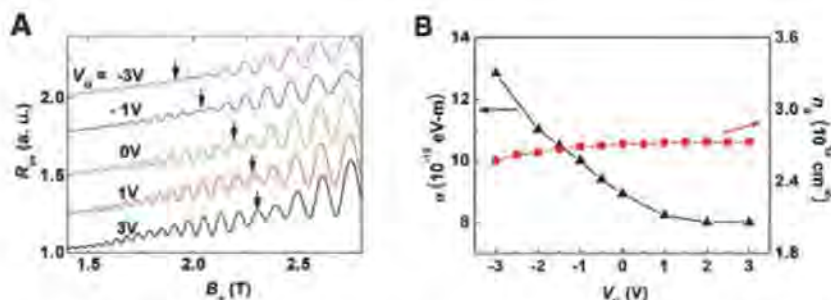


Fig. 2. Gate control of spin-orbit interaction at $T = 1.8$ K. (A) SdH oscillations as a function of gate voltage. The channel resistance R_{xx} is measured with a magnetic field, B_a , that is perpendicular to the 2DEG plane. (B) Spin-orbit interaction parameter α , deduced from (A), and carrier concentration n_s , as functions of gate voltage. Because of the asymmetry of the quantum well structure, α is nonzero at $V_G = 0$.

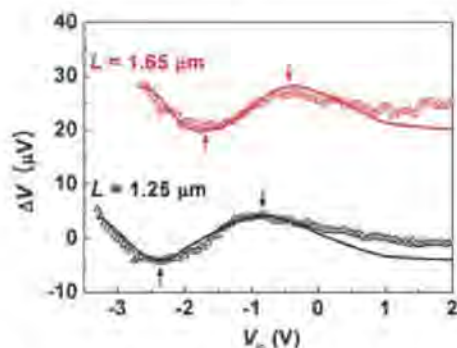


Fig. 3. Gate voltage modulation of spin FETs having different channel lengths, with $T = 1.8$ K and $I = 1$ mA. The symbols indicate experimental data. The solid lines are the fits obtained from Eq. 1. Data are offset for clarity. Baseline voltages are 1.032 mV and 0.715 mV for $L = 1.25 \mu\text{m}$ and $1.65 \mu\text{m}$, respectively.

A set of experiments was performed to enable quantitative analysis and detailed comparison with theory. Data from a conventional lateral spin valve measurement (5, 6, 8–12) are shown in Fig. 1E. In the absence of an external magnetic field, the magnetizations of the injector and detector have bistable states along the $\pm y$ axis because of their shape anisotropy, and they have slightly different coercivities because of the different aspect ratios. With $V_G = 0$ and constant bias current $I = 1$ mA, a small magnetic field was swept along the y axis, the magnetization alignment of FM electrodes changed between parallel and antiparallel configurations, and the detector voltage V was high or low, respectively. The characteristic dips seen in the data were observed for $B_a > 0$, when the field sweep was from negative to positive (black trace), and for $B_a < 0$, when the field sweep was from positive to negative (red trace). The spacing L between the injector and the detector is less than a carrier mean free path, l , and measurements are dominated by ballistic transport effects. There is no formal theory for the magnitude of the lateral spin valve effect for ballistic carriers. Instead, this conventional lateral spin valve measurement provides a calibration for the amplitude of the voltage os-

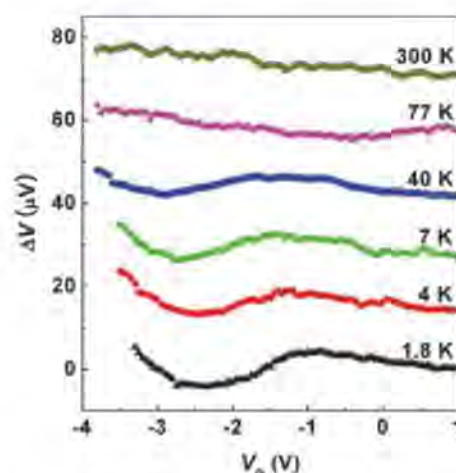


Fig. 4. Temperature dependence of oscillatory conductance with $L = 1.25 \mu\text{m}$ and $I = 1$ mA. As temperature increases, the mean free path decreases and transport characteristics change from ballistic to diffusive.

cillation in Fig. 1D, because the mechanism for spin-dependent voltage is the same for both experiments. The magnitude of the dips, $A \equiv \Delta V = 6 \pm 0.2 \mu\text{V}$, is the same as the amplitude of the oscillatory voltage shown in Fig. 1D, $\Delta V = 6 \pm 0.5 \mu\text{V}$, and this empirically measured amplitude A was used for the quantitative fits.

Next, the spin-orbit coupling strength α was measured as a function of gate voltage. SdH oscillations (17, 18) were measured at a variety of gate voltage values, beat patterns were observed (Fig. 2A), and $\alpha(V_G)$ was deduced (SOM text S2). The changing nodal position of the beat pattern (arrows in Fig. 2A) shows that the gate voltage strongly affects the spin-orbit coupling of carriers in the InAs single-quantum well. The magnitude of $\alpha(V_G)$ is strongly dependent on V_G for the range $-3 \leq V_G \leq 1$ V (Fig. 2B). The effect of the gate voltage is enhanced for the negative V_G because of nonlinear bending of the quantum well. The dependence of α on V_G is weak for the positive range $1 \leq V_G \leq 3$ V. Although magneto-intersubband scattering may also cause an oscillatory magnetoresistance (19, 20), this mechanism can be excluded from an interpretation of our data

by using a detailed analysis of the Fourier transforms of the SdH oscillations (SOM text S3). Because the gate voltage might be expected to change the carrier concentration in the channel, the voltage-dependent concentration $n(V_G)$ was directly determined from Hall measurements. It shows negligible variation over the experimental range of V_G (Fig. 2B). Having measured $\alpha(V_G)$, the magnitude of the Rashba field is readily calculated from $B_{Ry} = 2\alpha k_F / (g\mu_B)$ (1), where k_F and g are the Fermi wave vector and g factor, respectively, of the carriers in the channel, and $\mu_B = 9.27 \times 10^{-24}$ J/T is the Bohr magneton. Using $k_F = 4.13 \times 10^6 \text{ cm}^{-1}$ and $g = 15$ (21), the field at zero gate voltage (Fig. 2B) has magnitude $B_{Ry} = 8.5$ T. $B_a = 0.5$ T is an order of magnitude smaller than B_R and has a negligible effect on spin precession.

The theory of Datta and Das describes the transport of ballistic electrons in a 2DEG channel (SOM text S4). Allowing for an arbitrary phase shift φ , the expression for the detector voltage is

$$V = A \cos(2m^* \alpha L / \hbar^2 + \varphi) \quad (1)$$

The fit for the sample with $L = 1.65 \mu\text{m}$ and $m^* = 0.05m_0$ (22), where m_0 is 9.1×10^{-31} kg and $\hbar$ is Planck's constant divided by 2π , using the empirical values of $\alpha(V_G)$ and A , is plotted in Fig. 3 as a solid line and shows excellent quantitative agreement with the data. The phase shift φ , believed to be a consequence of shielding near the metallic ferromagnetic electrodes, is the only adjustable fitting parameter. The data fit well for more than a full wavelength of oscillation, with a small weakness of the fit occurring for the regime where gate voltage modulation of α is weak, $V_G > 0$ V.

Because precessional phase accumulation is proportional to L , it follows that carriers in a device with shorter spacing L will require a larger range of α , and therefore a larger range of gate voltage V_G to precess by π radians. A sample with $L = 1.25 \mu\text{m}$ was fabricated and the data and fit are shown as the bottom trace in Fig. 3. The half period of oscillation is seen to increase from $\Delta V_G = 1.24$ V ($L = 1.65 \mu\text{m}$) to $\Delta V_G = 1.53$ V ($L = 1.25 \mu\text{m}$). Data with different values of L are fit successfully by Eq. 1 with no adjustable parameter other than a small phase shift.

The temperature dependence of the oscillatory voltage is shown in Fig. 4. Gate voltage modulation is clearly observed up to $T = 40$ K. From the Dyakonov-Kachorovskii (23) and Dyakonov-Perel (24) mechanisms, the spin relaxation rate $1/\tau_s$ scales as $TE_1^2\tau_p$ in a narrow quantum well such as ours. Here E_1 is the confinement energy of the quantum well and τ_p is the momentum scattering time. In our experiments, τ_p is nearly proportional to $1/T$, and therefore the additional spin relaxation at higher temperature is negligible (6). At high temperatures, however, inelastic scat-

tering becomes more pronounced. Our measurements of the temperature dependence of the mean free path (SOM text S5) show that the conductance oscillation broadens and disappears in the same temperature range ($T \geq 40$ K) where l becomes shorter and transport therefore changes from ballistic to diffusive. This temperature dependence is a further confirmation of theory (1).

Two decades ago, Datta and Das proposed an experiment involving spin injection, detection, and spin precession caused by a gate voltage and special relativistic effects on ballistic electrons in a 2DEG. Separate aspects have been demonstrated individually (3, 5, 17). We have used the nonlocal lateral spin valve geometry to combine these aspects in a single experiment. The InAs single-quantum well used here is an ideal material, because a large spin-orbit interaction modulates a Rashba field by several teslas with a gate voltage range of a few volts.

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Materials and Methods

SOM Text

Figs. S1 to S5

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Memory Metamaterials

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The resonant elements that grant metamaterials their distinct properties have the fundamental limitation of restricting their useable frequency bandwidth. The development of frequency-agile metamaterials has helped to alleviate these bandwidth restrictions by allowing real-time tuning of the metamaterial frequency response. We demonstrate electrically controlled persistent frequency tuning of a metamaterial, which allows the lasting modification of its response by using a transient stimulus. This work demonstrates a form of memory capacitance that interfaces metamaterials with a class of devices known collectively as memory devices.

The ability of metamaterials to create electromagnetic responses absent in nature has initiated the new research field of transformation optics (1, 2), which has applications ranging from electromagnetic cloaking (3) to subdiffraction imaging (4). Frequency-agile metamaterials, which allow one to adjust the electromagnetic response in real time, are emerging as an important part of this field. The hybrid-metamaterial approach (5, 6), in which natural materials are integrated into the metamaterial composite, has been particularly successful in enabling frequency-agile metamaterials that respond to the application of voltage (7, 8), external electric field (9), light (10, 11), and heat (12). This tuning ability helps make metamaterial devices more versatile, adapting to shifting input or

changing target parameters. However, those methods for enabling frequency-agile metamaterials require the continuous application of an external stimulus to maintain altered metamaterial properties. Once the external stimulus is removed, the metamaterial returns to its original response. Essentially, any functionality derived from metamaterials would benefit greatly if the metamaterial tuning persisted once the triggering stimulus disappeared. Metamaterials that are tuned mechanically or geometrically should retain their tuned properties (13, 14), but such techniques are likely to be difficult to implement at higher frequencies or for complex designs. We have achieved an electrically controlled memory effect using a hybrid device composed of a resonant metamaterial and a transition metal oxide. The principle underlying the persistent tuning of our hybrid device is that of memory-capacitance (memcapacitance for short), which was recently suggested theoretically (15).

The persistent frequency tuning of a memory metamaterial device can be illustrated by use of a single-layer gold split-ring resonator (SRR) array patterned (16) on a 90-nm-thin film of vanadium dioxide (VO₂) (Fig. 1A). VO₂ is a correlated electron material that exhibits an insulator-to-metal (IMT) phase transition that can be thermally (17), electrically (9, 18), or optically (19) controlled.

The IMT is percolative in nature and is initiated by the formation of nanoscale metallic puddles in the insulating host (20). The transition is highly hysteretic and has been previously shown to exhibit memory effects (21). The hysteresis associated with the VO₂ can be observed by measuring the dc resistance of the sample (Fig. 1B, solid lines). The phase transition also affects the dielectric properties of VO₂ in a specific way. At the onset of the IMT, electronic correlations acting in concert with the spatial inhomogeneity of VO₂ create a sharply divergent permittivity (12, 20). This increasing VO₂ permittivity increases the capacitance of the SRR resonators so that the metamaterial resonance frequency decreases as the IMT progresses. The data in Fig. 1, B and C, illustrate this effect. At room temperature, we identify the resonance frequency of the SRR array as the spectral minimum at $\omega_0 = 1.65$ THz (Fig. 1C, darkest line). As the dielectric constant of VO₂ is increased with temperature, the resonance frequency red-shifts by as much as 20%. We show that this metamaterial resonance tuning persists when accomplished via short current pulses.

Because both the dc resistance and the permittivity are products of the IMT, the SRR resonance in the hybrid metamaterial inherits the same hysteretic nature observed in the dc resistance (21). Any transient excitation that causes a small perturbation in the VO₂ IMT will leave a lasting change of the resonance of the metamaterial. We can apply such an excitation voltage pulse using the electrical leads connected to the device. In this case, the applied voltage promotes the IMT by inducing local heating as current flows through the VO₂ film (22). In order to maximize the observable effect that small voltage pulses have on the metamaterial, we adjusted the temperature of the device to a range in which the hysteresis is most pronounced. This corresponds to a range in which the slope of the resistance as a function of temperature, $R(T)$, is the steepest,

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and we chose 338.6 K (Fig. 1B, dashed line). Applying a series of voltage pulses (Fig. 2B) while spectroscopically monitoring the resonance frequency of our hybrid structure before and after each pulse (12), we were able to see the effect of these sequential voltage pulses (Fig. 2A). Each pulse consistently red-shifts the resonance frequency. This red shift is clearly visible even after the voltage is removed, demonstrating that a persistent change in the hybrid metamaterial was obtained. The volumetric heat capacity of the whole device is quite large given the rather limited power input with each pulse. Thus, this is not a global thermal effect; rather, heating is localized primarily to the VO₂ film and is transient. After the voltage pulse subsides, the device rapidly thermalizes back to the starting temperature. Temperature monitoring confirmed that the overall temperature was unchanged to within ± 0.02 K during the entire duration of the experiment. The persistence of the modified resonance has been spectroscopically monitored for 10 min and did not show signs of degradation. Our work on the dc memory resistance of VO₂ suggests that the effect will persist much longer (21).

It is instructive to analyze the response of our device within an effective circuit model (23, 24). Our SRR array can be modeled as an array of RLC circuit elements, each with resonance frequency $\omega = (LC)^{-1/2}$ (Fig. 2C). The inductance L is known to remain constant because no permeability changes occur in any material within our device. This allows us to relate changes of the observed resonant frequency directly to a variation in capacitance: $\frac{C}{C_0} = \left(\frac{\omega_0}{\omega}\right)^2$. We estimate the capacitance C_0 of a single SRR of our dimensions as $C_0 \approx 2.5 \times 10^{-15}$ Farad/SRR (25). The green points in Fig. 2A show the SRR capacitance in this manner. The plotted capacitance C is the total capacitance of each SRR. To model the

persistent-tuning behavior of our device within the effective circuit picture, we introduced the circuit element of memory capacitance C_m (15), defined by the relations $q(t) = C_m(x, V_c, t)V_c(t)$ and $\dot{x} = f(x, V_c, t)$. V_c and $q(t)$ are the bias and charge, respectively, on the capacitor defined by VO₂, and x is a set of state variables that in the present case accounts for the dielectric behavior of the VO₂ IMT. C_m acts in parallel with the SRR natural capacitance to give a total capacitance of $C = C_0 + C_m$. In particular, C_m parameterizes the metamaterial-tuning memory effect demonstrated in Fig. 2A. The increasing conductivity of VO₂ as the IMT progresses also introduces a memory resistance (R_m) (Fig. 2B) [(15, 26) and references therein]. R_m acts detrimentally to reduce the quality factor of the metamaterial resonance in our device. Thus, softening of the resonance that accompanies the reduced resonance frequency is apparent in the spectra (Fig. 1C). In VO₂, the memory resistance and memory capacitance appear to be inextricably intertwined, which is an effect that has also been anticipated theoretically and should be particularly relevant at the nanoscale (15). In our circuit model, V_{ext} is the applied voltage pulse that modifies C_m and R_m . V_{IR} originates from our infrared probe. Very different powers and time scales allow us to effectively separate the operation of the probing V_{IR} and modifying V_{ext} into the SRR- and VO₂-dominated groups (Fig. 2C). Specifically, the resonance frequency of the SRRs is much faster than the time scales of V_{ext} , and the power levels used for spectroscopic probing are much less than those necessary for the modification of C_m . Systems in which these conditions are not true will make interesting nonlinear study cases.

To better illustrate the operation of the device, we propose a thermal finite-element model (16) to examine the time-evolution of the VO₂ temperature for a range of input powers (Fig. 3A). The

input power of the first four voltage pulses (α , β , γ , and δ) are marked, and for each a near steady-state rise in temperature (ΔT) quickly emerges. This thermal result enables a more detailed look at the evolution of capacitance during voltage pulses (Fig. 3B). Starting from data point A, with normalized capacitance $C = C_0$, the voltage pulse α raises the temperature of the VO₂ by $\Delta T_0 = 0.11$ K (as documented by the finite-element simulations), causing an increase in the capacitance. Once the voltage pulse stops, the VO₂ quickly (≤ 25 ms) (16) thermalizes back to the bias temperature of 338.6 K. However, because of the hysteresis in the IMT a net change in the capacitance persists, and the device settles to point B with capacitance $C = 1.006 C_0$. These simulations reveal the complete heating/cooling cycle, which gives the switching time scale as set by the thermal geometry of the device close to ~ 50 ms. The arrows in Fig. 3B illustrate this hysteretic capacitance behavior by showing a probable path for $C(T)$ during this heating/cooling cycle between data points. These arrows were drawn by using the experimentally determined pre- and post-pulse capacitances from Fig. 2A, and the maximum temperature rise was revealed from simulations in Fig. 3A. This is coupled with an assumption that the hysteresis in the IMT is strong enough that the post-pulse thermalization cooling has little effect on the capacitance value. This latter assumption is well-supported by the much flatter slope observed in Fig. 1B for the dc resistance during cooling than heating at 338.6 K ($dR_{\text{heat}}/dT = 100$ kilohm per degree Kelvin and $dR_{\text{cool}}/dT = 4$ kilohm per degree Kelvin, where R_{heat} is the resistance during heating and R_{cool} is the resistance during cooling), as well as other work (21). However, with our current equipment configuration we are unable to experimentally probe the capacitance on time scales that are fast enough to directly obtain this

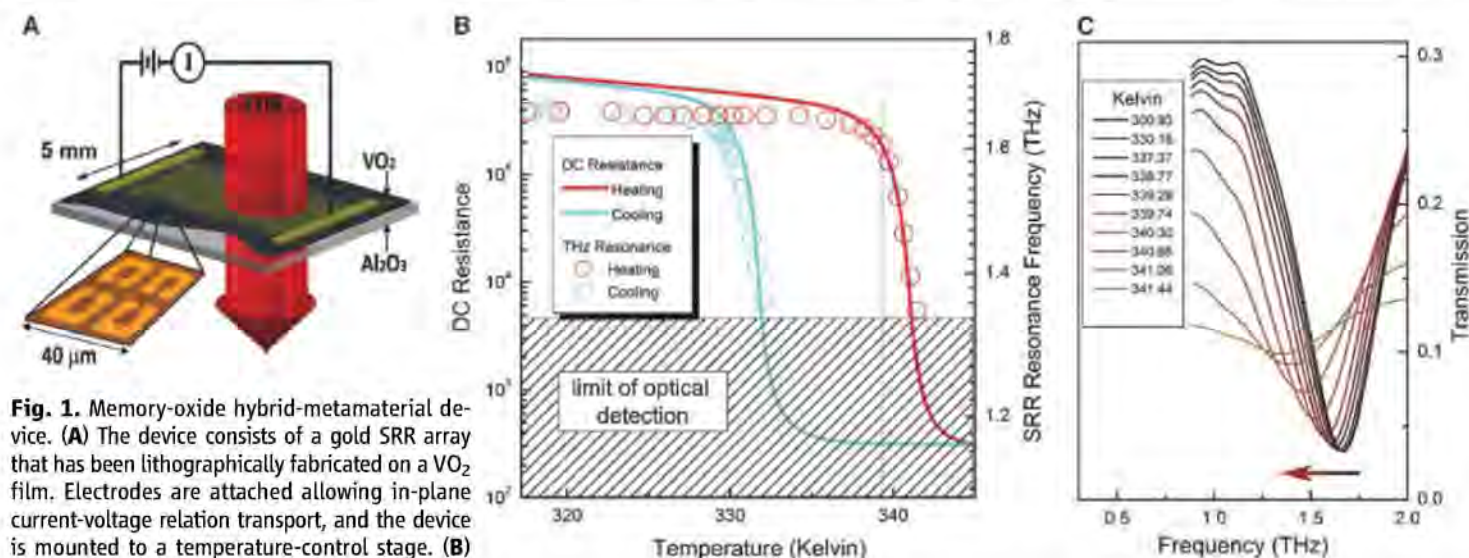


Fig. 1. Memory-oxide hybrid-metamaterial device. (A) The device consists of a gold SRR array that has been lithographically fabricated on a VO₂ film. Electrodes are attached allowing in-plane current-voltage relation transport, and the device is mounted to a temperature-control stage. (B) Simultaneous dc-transport and Far-infrared probing of the metamaterial demonstrate that as VO₂ passes through its insulator-to-metal transition, resistance drops and the SRR resonance frequency decreases. This latter effect occurs because of an increase in the per-SRR capacitance. (C) Spectroscopic data from which the metamaterial reso-

nance frequencies in (B) are identified (heating cycle shown). Data in (B) and (C) were obtained by performing a complete temperature cycle (300 to 350 to 300 K) with the temperature stage on which the sample is mounted.

$C(T)$ data inside pulses. Nevertheless, it is clear that the demonstration of electrically controlled memory capacitance in this device relies on the hysteretic nature of the VO_2 phase transition.

We stress that the use of a temperature bias in our experiment is required only to put a particular VO_2 film into a regime in which the IMT is highly hysteretic, although our VO_2 does exhibit some

hysteretic qualities even at room temperature (16). More promisingly, several VO_2 fabrication techniques are known to reduce the phase-transition temperature down to room temperature (27, 28) and thus will enable VO_2 -hybrid memory metamaterials to operate at ambient conditions. Additionally, any material that possesses a hysteretic response in either its permittivity or permeability

at a suitable frequency range could be used in a hybrid-metamaterial design so as to obtain memory effects analogous to those we demonstrated here (29). The correlated electron state that gives VO_2 the divergent permittivity used in this demonstration is only effective up to mid-infrared. A combination of other hysteretic materials with metamaterials operational in the near-infrared and visi-

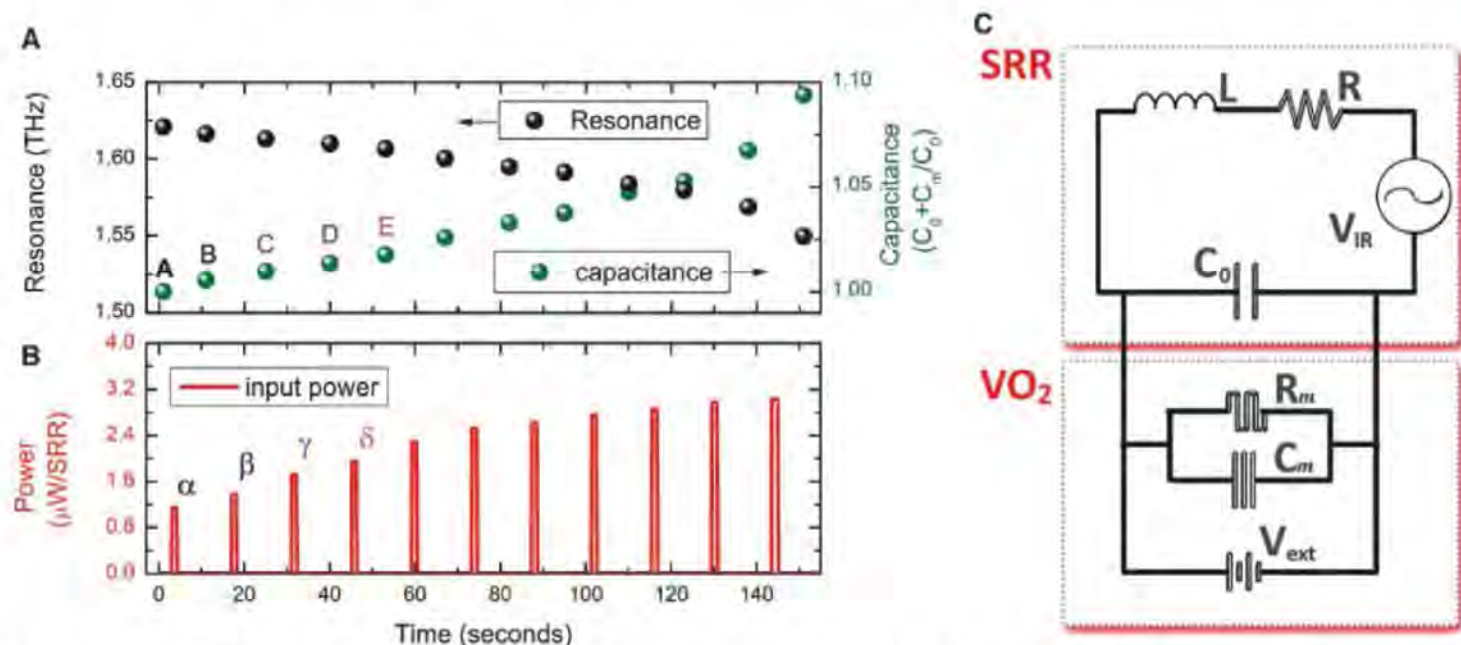


Fig. 2. Persistent electrical tuning of a metamaterial. (A) Successive modification of the resonance of the hybrid-metamaterial is achieved by sequential transient 1-s electrical pulses of increasing power. (B) These modifications persist until the device is thermally reset and have

been measured to be stable over 20 min. This operation is well illustrated within the effective circuit model (C) by the addition of memory circuit elements R_m and C_m in parallel to the natural capacitance of the SRR.

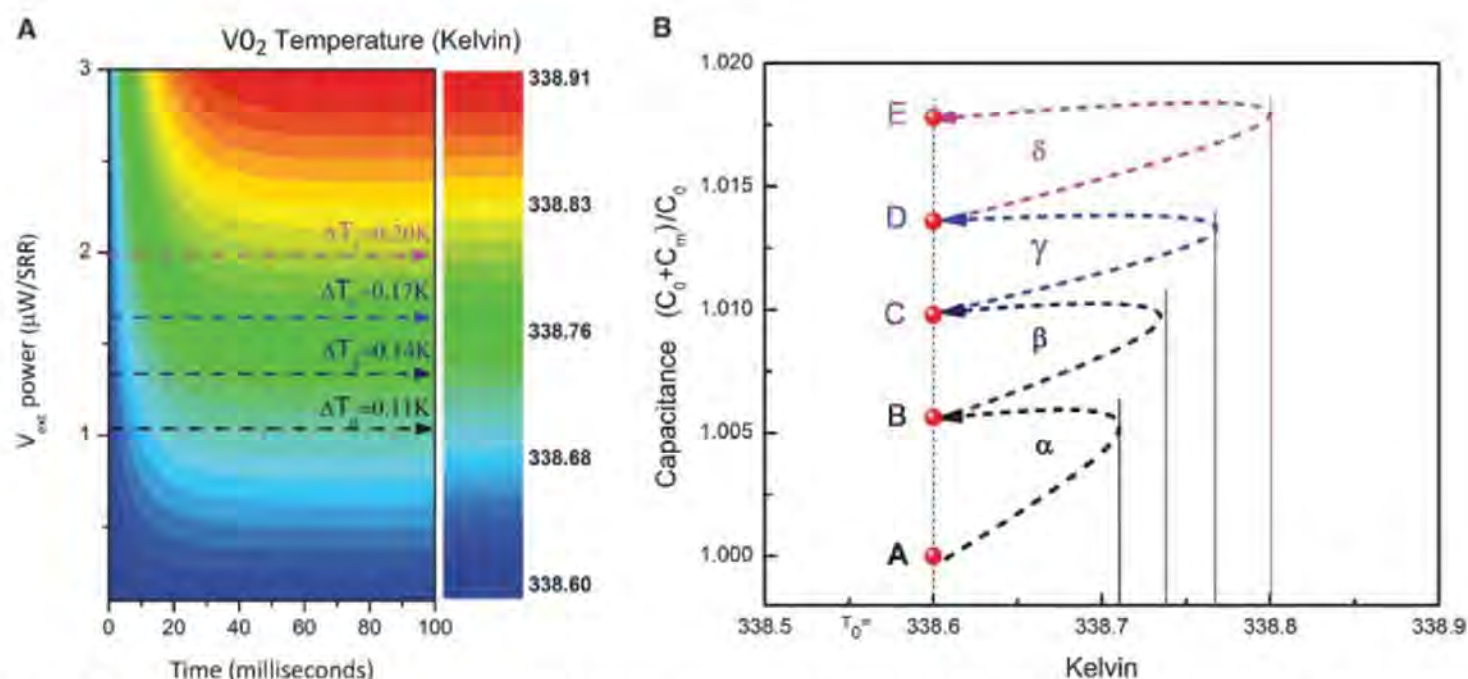


Fig. 3. The operation of memory capacitance explained via hysteretic phase transition. (A) Using a finite element model of our device, we calculated the temperature rise ΔT of the VO_2 film for a range of given input powers, including the first four voltage pulses in our experiment

(α , β , γ , and δ). A steady-state temperature rise was observed to emerge quite quickly. (B) This temperature rise was used in combination with data from Fig. 2A to estimate and sketch the behavior of capacitance during heating and cooling.

ble spectra could easily push this effect to higher frequencies that are beneficial for a variety of practical applications (30).

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Supporting Online Material

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Materials and Methods

Fig. S1

Table S1

References

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Itinerant Ferromagnetism in a Fermi Gas of Ultracold Atoms

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Can a gas of spin-up and spin-down fermions become ferromagnetic because of repulsive interactions? We addressed this question, for which there is not yet a definitive theoretical answer, in an experiment with an ultracold two-component Fermi gas. The observation of nonmonotonic behavior of lifetime, kinetic energy, and size for increasing repulsive interactions provides strong evidence for a phase transition to a ferromagnetic state. Our observations imply that itinerant ferromagnetism of delocalized fermions is possible without lattice and band structure, and our data validate the most basic model for ferromagnetism introduced by Stoner.

Magnetism is a macroscopic phenomenon with its origin deeply rooted in quantum mechanics. In condensed-matter physics, there are two paradigms for magnetism: localized spins interacting via tunneling and delocalized spins interacting via an exchange energy. The latter gives rise to itinerant ferromagnetism, which is responsible for the properties of transition metals such as cobalt, iron, and nickel. Both kinds of magnetism involve strong correlations and/or strong interactions and are not yet completely understood. For localized spins, the interplay of magnetism with d-wave superfluidity and the properties of frustrated spin materials are topics of current research. For itinerant ferromagnetism (1–7), phase transition theories are still qualitative.

We implemented the Stoner model, a textbook Hamiltonian for itinerant ferromagnetism (8), by using a two-component gas of free fer-

mions with short-range repulsive interactions, which can capture the essence of the screened Coulomb interaction in electron gases (8). However, there is no proof so far that this simple model for ferromagnetism is consistent when the strong interactions are treated beyond mean-field approaches. It is known that this model fails in one dimension, where the ground state is singlet for arbitrary interactions, or for two particles in any dimension (3). In our work, cold atoms were used to perform a quantum simulation of this model Hamiltonian in three dimensions, and we showed experimentally that this Hamiltonian leads to a ferromagnetic phase transition (2). This model was also realized in helium-3 (9), but the liquid turn into a solid phase and not into a ferromagnetic phase at high pressure. It has also been applied to neutrons in neutron stars (10).

To date, magnetism in ultracold gases has been studied only for spinor (11, 12) and dipolar (13) Bose-Einstein condensates (BECs). In these cases, magnetism is driven by weak spin-dependent interactions, which nevertheless determine the structure of the condensate because of a bosonic enhancement factor. In contrast, here we describe the simulation of quantum magnetism in a strongly interacting Fermi gas.

An important recent development in cold atom science has been the realization of superfluidity and the BEC–Bardeen-Cooper-Schrieffer (BCS) crossover in strongly interacting, two-component Fermi gases near a Feshbach resonance (14). These phenomena occur for attractive interactions for negative scattering length and for bound molecules (corresponding to a positive scattering length for two unpaired atoms). Very little attention has been given to the region of atoms with strongly repulsive interactions. One reason is that this region is an excited branch, which is unstable against near-resonant three-body recombination into weakly bound molecules. Nevertheless, many theoretical papers have proposed a two-component Fermi gas near a Feshbach resonance as a model system for itinerant ferromagnetism (15–22), assuming that the decay into molecules can be sufficiently suppressed. Another open question is the possibility of a fundamental limit for repulsive interactions. Such a limit due to unitarity or many-body physics may be lower than the value required for the transition to a ferromagnetic state. We show that this is not the case and that there is a window of metastability where the onset of ferromagnetism can be observed.

A simple mean-field model captures many qualitative features of the expected phase transition but is not adequate for a quantitative description of the strongly interacting regime. The total energy of a two-component Fermi gas of average density n (per spin component) in a volume V is given by $E_F 2Vn \left\{ \frac{3}{10} [(1 + \eta)^{5/3} + (1 - \eta)^{5/3}] + \frac{2}{3\pi} k_F a (1 + \eta)(1 - \eta) \right\}$, where E_F is the Fermi energy of a gas, k_F is the Fermi wave vector of a gas, a is the scattering length characterizing short-range interactions between the two components, and $\eta = \Delta n/n = (n_1 - n_2)/(n_1 + n_2)$ is the magnetization of the Fermi gas. The local magnetization of the Fermi gas is nonzero when the gas separates into two volumes, where the densities n_1 and n_2 of the two spin states differ

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by $2\Delta n$. We studied an ensemble in which the number of atoms in each spin state is conserved. This is equivalent to a free electron gas at zero external magnetic field where the total magnetization is zero. The interaction term represents any short-range spin-independent potential. When the gas is fully polarized, it avoids the repulsive interaction but increases its kinetic energy by a factor of $2^{2/3}$. The phase transition occurs when the minimum in energy is at nonzero magnetization (Fig. 1A) at $k_F a = \pi/2$. This onset was previously discussed in the context of phase separation in a two-component Fermi gas (15–18). Figure 1B shows several consequences of the phase transition for a system at constant pressure. First, for increasing repulsive interactions, the gas expands, lowering its density and Fermi energy; kinetic energy is therefore reduced. When the gas enters the ferromagnetic phase, kinetic energy increases rapidly because of the larger local density per spin state. Furthermore, the volume has a maximum value at the phase transition. This can be understood by noting that pressure in our model is $(2/3)E_{\text{kin}}/V + E_{\text{int}}/V$, where E_{kin} is kinetic energy and E_{int} is interaction energy. At the phase transition, the system increases its kinetic energy and reduces its interaction energy, thus reducing the pressure. This maximum in pressure at constant volume turns into a maximum in volume for a system held at constant pressure or in a trapping potential. We have observed three predictions of this model: (i) the onset of local magnetization through the suppression of inelastic collisions, (ii) the minimum in kinetic energy, and (iii) the maximum in the size of the cloud. These qualitative features are generic for the ferromagnetic phase transition and should also be present in more-advanced models (19).

We start with an atom cloud consisting of an equal mixture of ^6Li atoms in the lowest two hyperfine states, held at 590 G in an optical dipole trap with additional magnetic confinement (23). The number of atoms per spin state is approximately 6.5×10^5 , which corresponds to a Fermi temperature T_F of ~ 1.4 μK . The effective temperature T could be varied between $T/T_F = 0.1$ and $T/T_F = 0.6$ and was determined immediately after the field ramp by fitting the spatial distribution of the cloud with a finite temperature Thomas-Fermi profile. We define k_F^0 as the Fermi wave vector of the noninteracting gas calculated at the trap center. Applying the procedure discussed in (24) to repulsive interactions, we estimate that the real temperature is approximately 20% larger than the effective one. The effective temperature did not depend on $k_F^0 a$ for $k_F^0 a < 6$. At higher temperatures, additional shot-to-shot noise was caused by large fluctuations in the atom number. From the starting point at 590 G, the magnetic field was increased toward the Feshbach resonance at 834 G, thus providing adjustable repulsive interactions. Because of the limited lifetime of the strongly interacting gas, it was necessary to ap-

ply the fastest possible field ramp, limited to 4.5 ms by eddy currents. The ramp time is approximately equal to the inverse of the axial trap frequency (23) and therefore only marginally adiabatic. Depending on the magnetic field during observation, either atoms or atoms and molecules were detected by absorption imaging as described in fig. S1 (25).

The emergence of local spin polarization can be observed by the suppression of (either elastic or inelastic) collisions, because the Pauli exclusion principle forbids collisions in a fully polarized cloud. We monitored inelastic three-body collisions, which convert atoms into molecules. The rate (per atom) is proportional to $f(a, T)n_1 n_2$ or $f(a, T)n^2(1 - \eta^2)$ and is therefore a measure of the magnetization η . For $k_F a \ll 1$, the rate coefficient $f(a, T)$ is proportional to $a^6 \max(T, T_F)$ (26). This rate can be observed by monitoring the initial drop in the number of atoms during the first 2 ms after the field ramp. We avoided longer observation times, because the increasing molecule fraction could modify the properties of the sample.

A sharp peak appears in the atom loss rate around $k_F^0 a \approx 2.5$ at $T/T_F = 0.12$ (Fig. 2), indicating a transition in the sample to a state with local magnetization. The gradual decrease is consistent with the inhomogeneous density of the cloud, where the transition occurs first in the center. The large suppression of the loss rate indicates a large local magnetization of the cloud.

The kinetic energy of the cloud was determined by suddenly switching off the optical trap and the Feshbach fields immediately after the field ramp and then imaging state $|1\rangle$ atoms at zero field using the cycling transition after a ballistic expansion time of $\Delta t = 4.6$ ms. The kinetic energy was obtained from the Gaussian radial width σ_x as $E_{\text{kin}} = [(3m\sigma_x^2)/(2\Delta t^2)]$ where m is the mass of the ^6Li atom. A minimum of the kinetic energy at $k_F^0 a \approx 2.2$ for the coldest temperature $T/T_F = 0.12$ nearly coincided with

the onset of local polarization (Fig. 3). The peak in the atom loss rate occurs slightly later than the minimum of kinetic energy, probably because $f(a, T)$ increases with a (22). Because the temperature did not change around $k_F^0 a \approx 2.2$, the increase in kinetic energy is not caused by heating but by a sudden change in the properties of the gas, which is consistent with the onset of ferromagnetism. The observed increase in kinetic energy is approximately 20% at $T/T_F = 0.12$, smaller than the value $(2^{2/3} - 1) = 0.59$ predicted for a fully polarized gas. This discrepancy could be due to the absence of polarization or partial polarization in the wings of the cloud. Also, it is possible that the measured kinetic energy of the strongly interacting gas before the phase transition includes some interaction energy if the Feshbach fields are not suddenly switched off. For the current switch-off time of ~ 100 μs , this should be only a 5% effect, but the magnetic field decay may be slower because of eddy currents.

Finally, Fig. 4 shows our observation of a maximum cloud size at the phase transition, in agreement with the prediction of the model. The cloud size may not have fully equilibrated, because our ramp time was only marginally adiabatic, but this alone cannot explain the observed maximum.

The suppression of the atom loss rate, the minimum in kinetic energy, and the maximum in cloud size show a strong temperature dependence between $T/T_F = 0.12$ and 0.22. The properties of a normal Fermi gas approaching the unitarity limit with $k_F^0 a \gg 1$ should be insensitive to temperature variations in this range; therefore, the observed temperature dependence provides further evidence for a transition to a new phase.

At higher temperature (e.g., $T/T_F = 0.39$ as shown in Fig. 3), the observed nonmonotonic behavior becomes less pronounced and shifts to larger values of $k_F^0 a$ for $3 \leq k_F^0 a \leq 6$. For all three observed properties (Figs. 2 to 4), a nonmonotonic behavior is no longer observed at $T/T_F = 0.55$ (27). One interpretation is that at this temperature and

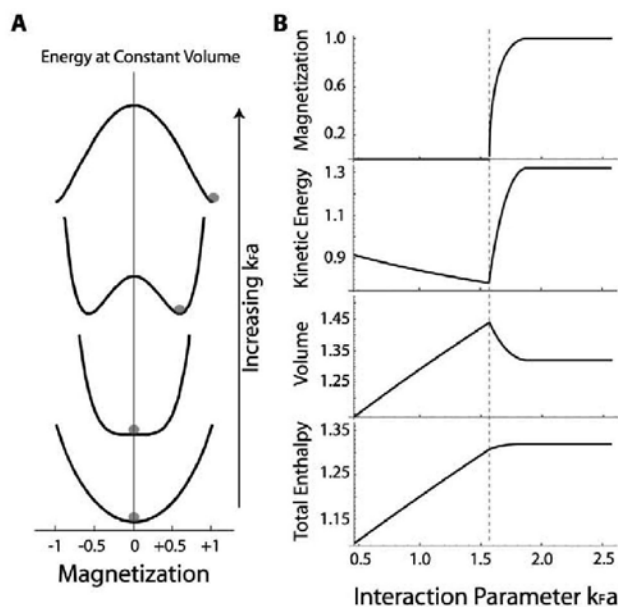


Fig. 1. Ferromagnetic phase transition at $T = 0$, according to the mean-field model described in the text. The onset of itinerant ferromagnetism occurs when the energy as a function of magnetization flips from a U shape to a W shape (A). (B) Enthalpy, volume, and kinetic energy, normalized to their values for the ideal Fermi gas, and magnetization as a function of the interaction parameter $k_F a$. k_F is defined by the density of the gas. The dotted line marks the phase transition.

above, there is no longer a phase transition. In a mean-field approximation, a ferromagnetic phase would appear at all temperatures but for increasing values of $k_F a$. Our observations may imply that the interaction energy saturates around $k_F a \approx 5$.

The spin-polarized ferromagnetic state should not suffer from inelastic collisions. However, typical lifetimes were 10 to 20 ms, which were probably related to a small domain size and three-body recombination at domain walls.

Fig. 2. Atom loss rate as a probe for local spin polarization, for different temperatures. $T/T_F = 0.55$ (triangles, dashed curve), $T/T_F = 0.22$ (open circles, dotted curve), and $T/T_F = 0.12$ (solid circles, solid black curve). The curves are guides to the eye, based on the assumption of a loss rate that saturates for increasing a in the normal state. The shaded area around the phase transition at $T/T_F = 0.12$ highlights the same region as in Figs. 3 and 4.

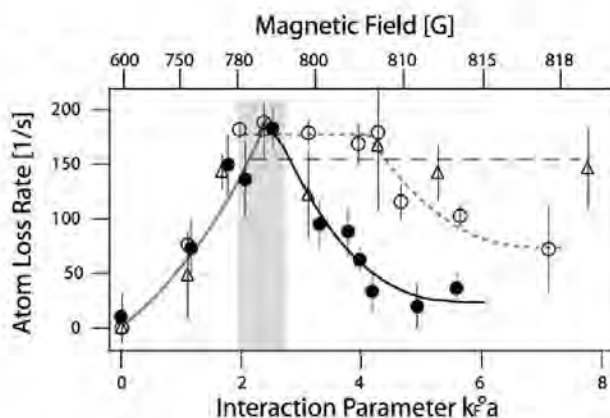
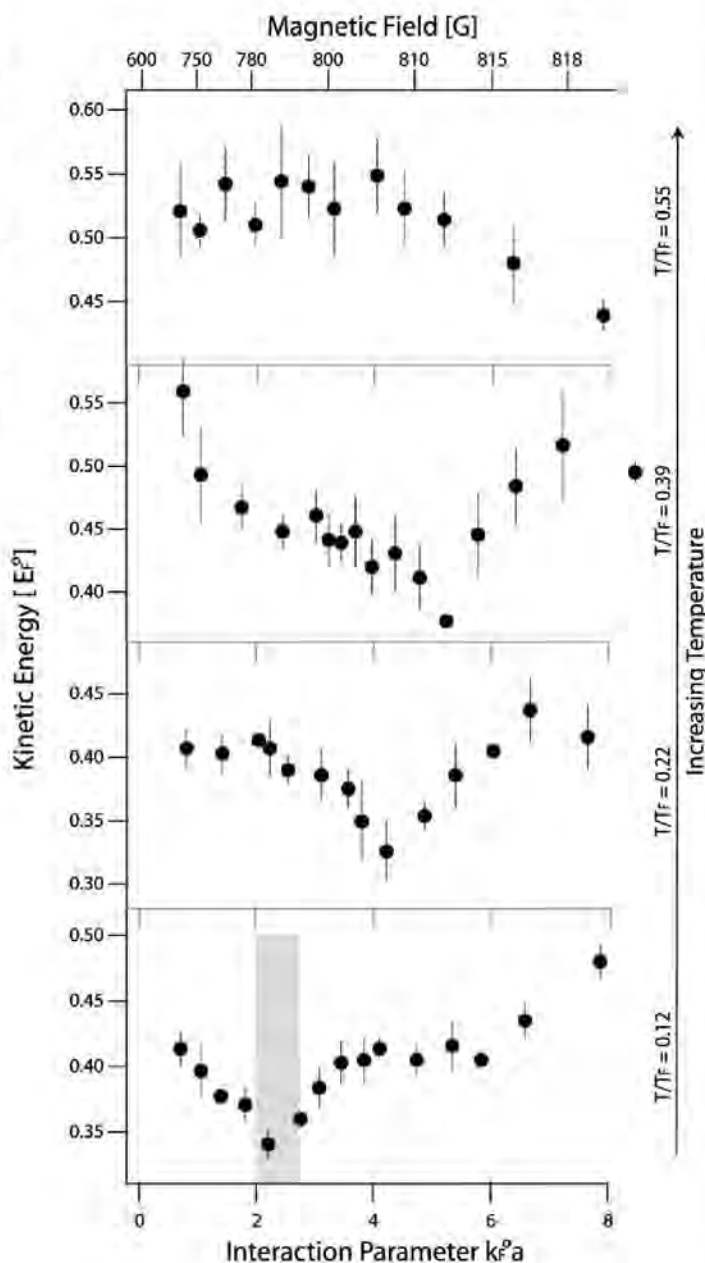


Fig. 3. Kinetic energy of a repulsively interacting Fermi gas determined for different interaction parameters $k_F^0 a$ and temperatures. The measured kinetic energy is normalized by the Fermi energy E_F^0 of the noninteracting Fermi gas at $T = 0$, calculated at the trap center with the same number of atoms per spin state. Each data point represents the average of three or four measurements.



We were unsuccessful in imaging ferromagnetic domains using differential in situ phase-contrast imaging (28). A signal-to-noise level of ~ 10 suggests that there were at least 100 domains in a volume given by our spatial resolution of $\sim 3 \mu\text{m}$ and by the radial size of the cloud. This implies that the maximum volume of the spin domains is $\sim 5 \mu\text{m}^3$, containing ~ 50 spin-polarized atoms. We suspect that the short lifetime prevented the domains from growing to a larger size and eventually adopting the equilibrium texture of the ground state, which has been predicted to have the spins pointing radially outward, like a hedgehog (20, 22). All our measurements are sensitive only to local spin polarization and are independent of domain structure and texture.

The only difference between our experiment and the ideal Stoner model is a molecular admixture of 25% (Fig. 4). The molecular fraction was constant for $k_F^0 a > 1.8$ for all temperatures and therefore cannot be responsible for the sudden change of behavior of the gas at $k_F^0 a \approx 2.2$ at the coldest temperature $T/T_F = 0.12$. This prediction was confirmed by repeating the kinetic energy measurements with a molecular admixture of 60%. The minimum in the kinetic energy occurred at the same value of $k_F^0 a$ within experimental accuracy.

For a comparison of the observed phase transition at $k_F^0 a \approx 2.2$ to the theoretical predictions, the ideal gas k_F^0 has to be replaced by the value for the interacting gas, which is smaller by $\sim 15\%$ because of the expansion of the cloud (Fig. 4), resulting in a critical value for $k_F a \approx 1.9 \pm 0.2$. At $T/T_F = 0.12$, the finite temperature correction in the critical value for $k_F a$ is predicted to be less than 5% (19). The observed value for $k_F a$ is larger than both the mean-field prediction of $\pi/2$ and the second-order prediction of 1.054 at zero temperature (19). Depending on the theoretical approach, the phase transition has been predicted to be first or second order. This could not be discerned in our experiment because of the inhomogeneous density of the cloud.

It has been speculated (19) that earlier experiments on the measurement of the interaction energy (29) and radio frequency spectroscopy of Fermi gases (30) showed evidence for the transition to a ferromagnetic state at or below $k_F a = 1$. This interpretation seems to be ruled out by our experiment.

Our work demonstrates a remarkable asymmetry between positive and negative scattering length. Early work (15) predicted that for $k_F |a| = \pi/2$, both an attractive and a repulsive Fermi gas become mechanically unstable (against collapse and phase separation, respectively). In an attractive Fermi gas, however, the mechanical instability does not occur [due to pairing (31)], in contrast to our observations in a repulsive Fermi gas. This suggests that the maximum total repulsive energy [in units of $3/5(2V/n)E_F$] is larger than the maximum attractive energy $|\beta|$ of 0.59 (32) that is realized for infinite a (23).

The interpretation of our results in terms of a phase transition to itinerant ferromagnetism is based on the agreement with the prediction of simplified models [Fig. 1, (15–22)]. Future

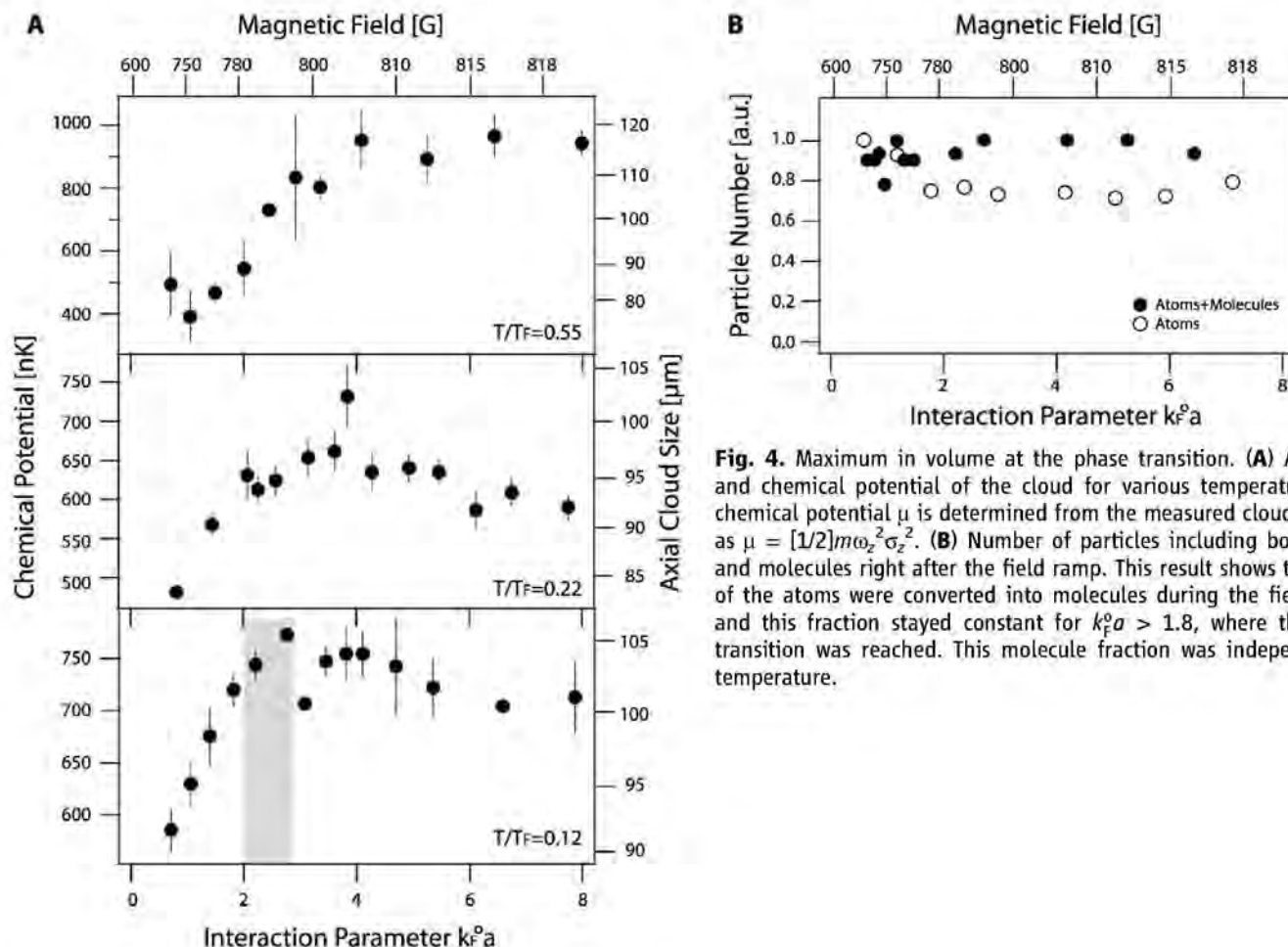


Fig. 4. Maximum in volume at the phase transition. **(A)** Axial size and chemical potential of the cloud for various temperatures. The chemical potential μ is determined from the measured cloud size, σ_z , as $\mu = [1/2]m\omega_z^2\sigma_z^2$. **(B)** Number of particles including both atoms and molecules right after the field ramp. This result shows that 25% of the atoms were converted into molecules during the field ramp, and this fraction stayed constant for $k_F a > 1.8$, where the phase transition was reached. This molecule fraction was independent of temperature.

work should address how the observed signatures are modified by strong interactions and correlations. Additional insight can be obtained by varying the magnetic field ramp time over a wide range and studying the relaxation toward an equilibrium state (33).

Heisenberg and Bloch's explanation for ferromagnetism was based on exchange energy; that is, the Pauli principle and spin-independent repulsive interactions between the electrons. However, it was unknown what other "ingredients" were needed for itinerant ferromagnetism. It was not until 1995 (6, 7) that a rigorous proof was given that, in certain lattices, spin-independent Coulomb interactions can give rise to ferromagnetism in itinerant electron systems. Our finding suggests that Heisenberg's idea does not require a lattice and band structure but already applies to a free gas with short-range interactions. Our experiment can be regarded as quantum simulation of a Hamiltonian for which even the existence of a phase transition was unproven. This underlines the potential of cold atom experiments as quantum simulators for many-body physics.

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An Anomalous Basaltic Meteorite from the Innermost Main Belt

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Triangulated observations of fireballs allow us to determine orbits and fall positions for meteorites. The great majority of basaltic meteorites are derived from the asteroid 4 Vesta. We report on a recent fall that has orbital properties and an oxygen isotope composition that suggest a distinct parent body. Although its orbit was almost entirely contained within Earth's orbit, modeling indicates that it originated from the innermost main belt. Because the meteorite parent body would likely be classified as a V-type asteroid, V-type precursors for basaltic meteorites unrelated to Vesta may reside in the inner main belt. This starting location is in agreement with predictions of a planetesimal evolution model that postulates the formation of differentiated asteroids in the terrestrial planet region, with surviving fragments concentrated in the innermost main belt.

Meteorites, except those coming from Mars or the Moon, record the conditions that existed during the formation of the solar system. They can be thoroughly analyzed in the laboratory, but there is virtually no constraint on where they come from. Although the value of combined orbital and compositional data is clear (1, 2), it remains difficult to recover those meteorites for which precise orbits have been determined. Of the 1076 documented meteorite falls that have been observed over the past several centuries (3), there are reliable orbits for only a handful (1). Dedicated observing networks, designed to image fireballs, triangulate trajectories, and determine orbits and fall positions, have succeeded in recovering four meteorites with orbits (1), but recovery rates from these networks are extremely low. Here, we report data on a meteorite recovered from the Nullarbor Desert of Australia after being recorded by the Desert Fireball Network (DFN) as it entered the atmosphere. The DFN is located in an area that has proved suitable for locating meteorites (4) and currently comprises four automated fireball observatories.

The fireball was observed over southwestern Australia on 20 July 2007 at $19^{\text{h}}13^{\text{m}}53.24^{\text{s}} \pm 0.05^{\text{s}}$ UT (the time of the beginning of the event), recorded by two eastern stations of the DFN (Fig. 1). The object, with initial mass of ~22 kg, began a luminous trajectory at an altitude of 62.83 km, and after a 64.7-km-long flight (which included

several fragmentation events) terminated at an altitude of 29.59 km. The most probable mass for the largest individual meteorite fragments calculated from our models was in the range 100 to 250 g. The search strategy was focused around the projected highest-probability fall line (5), bounded by these mass limits. The first stone (150 g) was found 97 m southward from the predicted central line; the second stone (174 g) was found 39 m northward from the central line. The meteorite is designated Bunburra Rockhole (BR) after a nearby landscape structure.

This first DFN sample is an igneous achondrite. Initial petrography indicated that BR is a brecciated eucrite containing numerous clasts; backscatter electron images revealed three lithologies delineated by grain size (fig. S1). Eucrites are part of a larger clan (the howardites, eucrites, and diogenites, or HEDs) that has been linked, via similarities in reflectance spectra, to asteroid 4 Vesta (6, 7). The lithological diversity and impact history of HED samples require them to have come from a relatively large parent body; 4 Vesta is the largest intact differentiated asteroid in the main belt.

However, BR is not a typical eucrite. It has a distinct oxygen isotopic composition, plotting significantly above the HED mass fractionation line

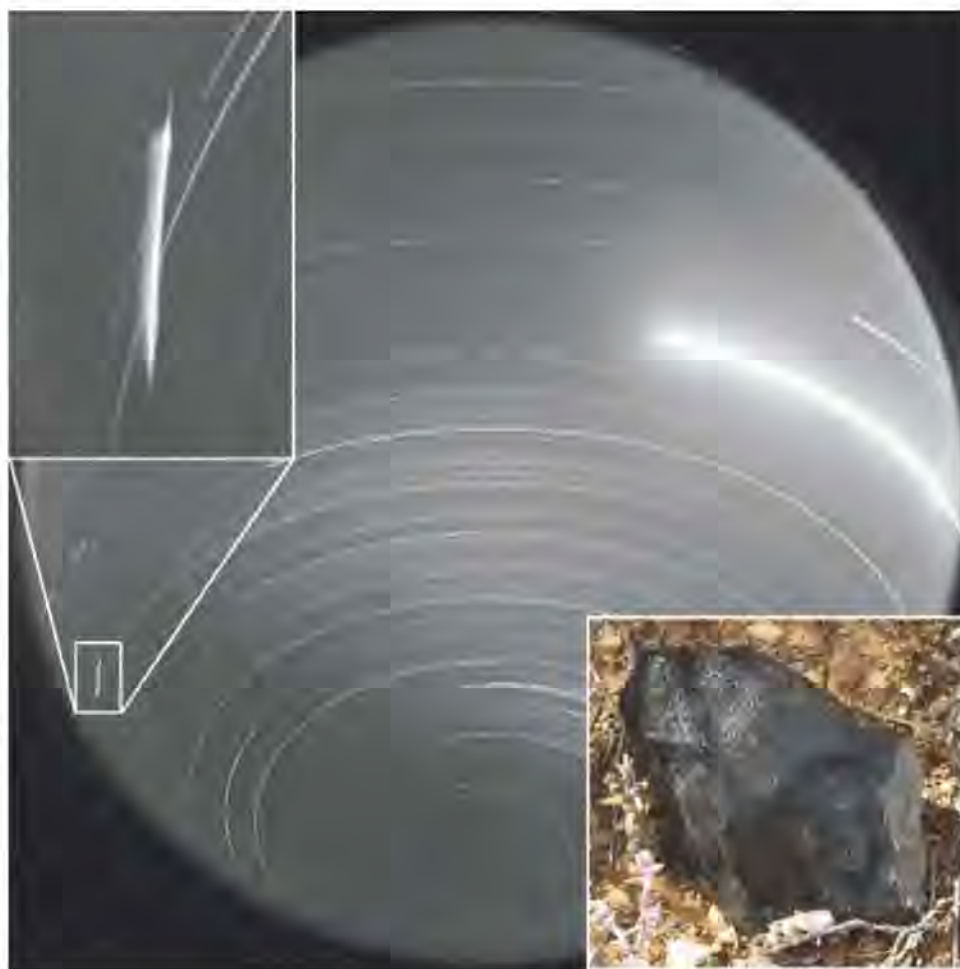


Fig. 1. All-sky image from the easternmost station in the Desert Fireball Network, showing the track of the fireball at left (and inset), close to the horizon, and Bunburra Rockhole (BR) at the recovery site (inset).

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(Fig. 2). North West Africa 011 (NWA 011, a meteorite found in the Sahara in 1999) was the first of these anomalous eucrite-like basaltic meteorites to be identified (8). On the basis of its unusual oxygen isotope composition, NWA 011 was presumed to derive from a basaltic parent asteroid other than 4 Vesta (8). NWA 011 has $\Delta^{17}\text{O} = -1.80$ per mil (‰) (8, 9), whereas HEDs define a mass fractionation line of $\Delta^{17}\text{O} = -0.242 \pm 0.016$ ‰ (2 σ) (10, 11). Data from nine replicate analyses (table S1), taken from coarse, medium, and fine textural subtypes, indicate that BR has $\Delta^{17}\text{O} = -0.112 \pm 0.042$ ‰ (2 σ) (Fig. 2). Following NWA 011, a further five anomalous eucrite-like basaltic meteorites were identified on the basis of their oxygen isotope compositions (and, in some cases, unusual mineralogy): Ibitira (a meteorite that fell in Minas Gerais, Brazil, in 1957), Asuka-881394 (found in the Queen Maud Land region of Antarctica, 1988), PCA 91007 (found in the Pescora Escarpment region of Antarctica, 1991), Pasamonte (fell in New Mexico, USA, 1933), and NWA 1240 (found in the Sahara, 2001) (11–15). Of these six, only three (Ibitira, Asuka-881394, and NWA 011) diverge sufficiently from the HED mass fractionation line to unambiguously require distinct parent asteroids (11). BR is the fourth.

BR also appears to be unusual among these anomalous achondrites in displaying substantial variations in $\Delta^{17}\text{O}$ values between lithological subtypes. The oxygen isotopic composition within other HEDs or anomalous eucrite-like basalts shows little heterogeneity [e.g., dark clast and light matrix in Pasamonte are virtually identical, with $\Delta^{17}\text{O}$ values of -0.198 ‰ and -0.206 ‰, respectively (11)]. In contrast, $\Delta^{17}\text{O}$ values in BR range from -0.092 ‰ in the fine-grained lithology to -0.131 ‰ in the coarse-grained lithology. The average $\Delta^{17}\text{O}$ value for BR is 0.112 ± 0.021 ‰ (1 σ), which is a larger 1 σ value than observed in any of the HEDs or anomalous eucrite-like basaltic achondrites analyzed in recent studies (11–13). The relatively high level of oxygen isotope heterogeneity displayed by BR lends further support to the suggestion that this meteorite comes from a separate source from that of other basaltic achondrites. It has been proposed that complete oxygen isotope homogenization on 4 Vesta occurred during an early-stage, large-scale melting event, which may equate with the development of a magma ocean (10). The oxygen isotope heterogeneity exhibited by BR indicates that its parent body may have experienced substantially less early-stage melting than 4 Vesta. By analogy with the primitive achondrites, it would indicate that the body had not completely equilibrated with respect to oxygen isotopes.

The major-element composition and mineralogy of the six anomalous eucrite-like basalts are similar to those of normal eucrites (with the exception of the Fe/Mn ratio for NWA 011 and Ibitira pyroxenes, and plagioclase composition in Asuka-881394). Likewise, BR has mineral composition (fig. S2) (16), mineral abundance (17), and petrography similar to those of normal eu-

crites. This suggests that different parent bodies had very similar histories. However, it has been shown that eucrite-like and angrite-like partial melts can be generated from the same starting material simply by changing oxygen fugacity (18): Eucritic melts are produced at low fugacities (IW-1), angritic melts at higher fugacities (IW+2). By extension, melts forming at similar oxygen fugacities but on different parent bodies may have similar major-element chemistries.

In the case of BR we have determined its orbit, which means we can trace its orbital history. BR was delivered from an unusual, Aten-type orbit (Fig. 3). Aten asteroids are near-Earth objects (NEOs) that have semimajor axes of <1 AU. In this case, virtually the entire orbit was contained within Earth's orbit (Fig. 3). Although orbital data for achondrites have been lacking, it has been suggested that symmetric ante meridiem and post meridiem achondrite fall times can

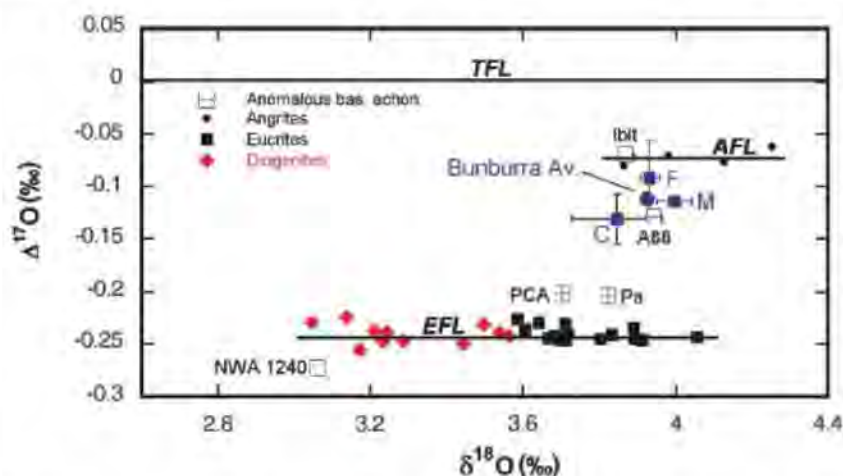
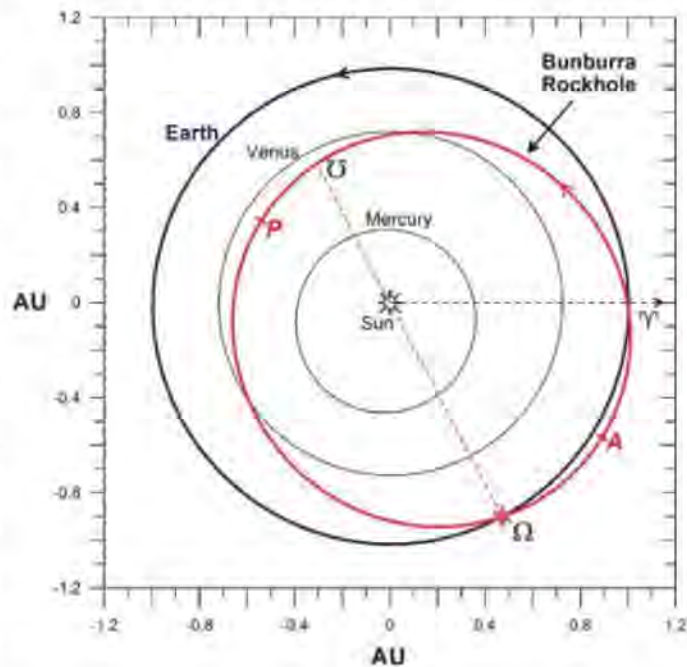


Fig. 2. Oxygen isotopic composition of BR relative to eucrites and diogenites (meteorites associated with 4 Vesta), the angrite group, and anomalous eucrite-like basaltic achondrites [other meteorite data from (10, 11)]. Three distinct lithologies are present in BR (C, coarse-grained; M, medium-grained; F, fine-grained), each having slightly different but overlapping oxygen isotope compositions. BR plots off the eucrite mass fractionation line (EFL) (10, 11). It also plots well away from the anomalous eucrite-like basalts NWA 1240, PCA 91007 (PCA), and Pasamonte (Pa). The BR fine-grained lithology shows slight overlap with the angrites and Ibitira (Ibit) in terms of $\Delta^{17}\text{O}$ values. Only the anomalous eucrite-like basalt A-881394 (A88) plots close to the BR average composition. TFL, terrestrial fractionation line; AFL, angrite fractionation line (10). Error bars are 2 σ .

Fig. 3. Orbit of BR projected on the plane of the ecliptic, with orbits of Earth, Venus, and Mercury. P and A are the positions of perihelion and aphelion, respectively, of the BR orbit; Ω and Υ are the ascending and descending nodes, showing which part of the orbit is above or below the plane of the ecliptic (the position of the ascending node also defines the collision point of BR with Earth); the arrow labeled Υ shows the direction to the point of equinox. Orbital parameters: initial velocity = 13.40 ± 0.02 km/s; semimajor axis = 0.8514 ± 0.0009 AU; argument of perihelion = $209.87^\circ \pm 0.11^\circ$; eccentricity = 0.2450 ± 0.0013 ; longitude of ascending node = $297.59528^\circ \pm 0.00004^\circ$; perihelion distance = 0.6428 ± 0.0018 AU; inclination = $9.07^\circ \pm 0.07^\circ$; aphelion distance = 1.05996 ± 0.00012 AU; period = 0.7856 ± 0.0012 years. Angular elements are in J2000 equinox.



occur only if orbital maturity has been achieved (19, 20). The fact that BR was on a mature Aten orbit supports this suggestion. We explored BR's most recent orbital history, finding approaches as close as 0.04 AU (distance to within a factor of 2) for an encounter with Venus in September 2001, and earlier close approaches with Earth [a search for BR precursor objects in NEO space was also made (5)]. In addition, we used a numerical method designed to model the evolution of NEO orbits (21) to determine the probability that BR came from a specific NEO source region, given its present-day semimajor axis, eccentricity, and inclination (this approach is based on the assumption that small NEOs have the same orbital distribution as observed kilometer-sized NEOs). The probability of BR coming from the innermost region of the main belt is 98%. There is a 72% probability that it was delivered from the v_6 resonance, a 26% probability that it came from one of the numerous small resonances in the inner main belt, and a 2% probability that it came from the 3:1 resonance. The outer main belt (>2.8 AU) and the Jupiter-family comet population can be ruled out as possible sources.

The BR parent body would likely be classified as a V-type asteroid. The characteristics of a reflectance spectrum are largely controlled by the major-element chemistry of the dominant phases, principally pyroxene (7). Because the major-element composition of BR's pyroxene (and plagioclase) (fig. S2) (16), modal mineral abundance (17), and grain size (fig. S1) are similar to those of normal eucrites, the reflectance spectrum should also be very similar to that of normal eucrites (i.e., it should match that of V-type asteroids). There are few V-type asteroids that are dynamically distinct from 4 Vesta (22, 23). In the inner main belt, most V-types are part of the Vesta dynamical family [the proximity of a few V-types to resonances was a fundamental link in the conceptual chain connecting 4 Vesta with HED meteorites (3)]. Even for those inner main belt V-types that are not currently part of the Vesta dynamical family, it is difficult to exclude an origin at Vesta (24–26). In the case of BR, compositional as well as orbital data indicate that basaltic asteroids unrelated to 4 Vesta reside in the innermost main belt, and that these bodies are delivering material (most likely via the v_6 resonance) into Earth-crossing orbits.

Finally, the predicted source region of BR is consistent with a recent planetesimal evolution model (27). In this model, planetesimals forming in the terrestrial planet region, which would have had fast accretion times relative to main belt objects, would also have been more likely to melt (from decay of short-lived radionuclides such as ^{26}Al) than later-accreting chondrites. The collisional evolution of these planetesimals would result in fragments, some of which (according to numerical simulations) would have been scattered into the main belt via interactions with planetary embryos (27). The model provides an explanation both for the paucity of differentiated asteroids in

the main belt and for the anomalously old ages for differentiated meteorites [e.g., (28)]. The greatest concentration of surviving fragments should be in the innermost main belt (27), the most probable starting location for the BR precursor.

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Evidence for Obliquity Forcing of Glacial Termination II

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Variations in the intensity of high-latitude Northern Hemisphere summer insolation, driven largely by precession of the equinoxes, are widely thought to control the timing of Late Pleistocene glacial terminations. However, recently it has been suggested that changes in Earth's obliquity may be a more important mechanism. We present a new speleothem-based North Atlantic marine chronology that shows that the penultimate glacial termination (Termination II) commenced $141,000 \pm 2500$ years before the present, too early to be explained by Northern Hemisphere summer insolation but consistent with changes in Earth's obliquity. Our record reveals that Terminations I and II are separated by three obliquity cycles and that they started at near-identical obliquity phases.

During the Late Pleistocene, the period of glacial-to-interglacial transitions (or terminations) has increased relative to the Early Pleistocene [~ 100 thousand years (ky) versus 40 ky] (1, 2). A coherent explanation for this shift still eludes paleoclimatologists (3). Al-

though many different models have been proposed (4), the most widely accepted one invokes changes in the intensity of high-latitude Northern Hemisphere summer insolation (NHSI). These changes are driven largely by the precession of the equinoxes (5), which produces relatively large

seasonal and hemispheric insolation intensity anomalies as the month of perihelion shifts through its ~23-ky cycle.

Recently, a convincing case has been made for obliquity control of Late Pleistocene terminations (4), which is a feasible hypothesis because of the relatively large and persistent increases in total summer energy reaching the high latitudes of both hemispheres during times of maximum Earth tilt. Indeed, the obliquity period has been found to be an important spectral component in methane (CH_4) and paleotemperature records from Antarctic ice cores (6, 7).

Testing the obliquity and other orbital-forcing models requires precise chronologies through terminations, which are best recorded by oxygen isotope ratios of benthic foraminifera ($\delta^{18}\text{O}_b$) in deep-sea sediments (1, 8). Although affected by deep-water temperature (T_{dw}) and composition ($\delta^{18}\text{O}_{\text{dw}}$) variations triggered by changes in circulation patterns (9), $\delta^{18}\text{O}_b$ signatures remain the most robust measure of global ice-volume changes through terminations. Unfortunately, dating of marine sediment records beyond the limits of radiocarbon methods has long proved difficult, and only Termination I [T-I, ~18 to 9 thousand years ago (ka)] has a reliable independent chronology. Most marine chronologies for earlier terminations rely on the SPECMAP orbital template (8) with its a priori assumptions of insolation forcing and built-in phase lags between orbital trigger and ice-sheet response. Although SPECMAP and other orbital-based age models serve many important purposes in paleoceanography, their ability to test climate-forcing hypotheses is limited because they are not independent of the hypotheses being tested. Consequently, the inability to accurately date the benthic record of earlier terminations constitutes perhaps the single greatest obstacle to unraveling the problem of Late Pleistocene glaciations.

Of the pre-T-I Late Pleistocene terminations, Termination II (T-II) has generated greatest interest. Several previous attempts to establish its timing from radiometrically dated archives have challenged the NHSI model (10–12). Arguably, the best known is the Devils Hole (DH) vein calcite record (10), which placed the timing of T-II ~15 ky earlier than that of the SPECMAP model prediction. Although now considered to be a regional rather than a global paleoclimate proxy (13), it highlighted the potential of using

radiometrically datable archives to test climate-forcing hypotheses. Since then, radiometric ages on corals and detrital marine carbonates have been used to constrain sea levels during and immediately after T-II (11, 12, 14). However, this approach has proved controversial because of open-system effects on marine carbonate ages (15), which are difficult to deconvolve and correct (16).

To determine the age of T-II, we applied the uranium-thorium (U-Th) chronology from a high-resolution speleothem $\delta^{18}\text{O}$ time series to the T-II marine sediment record from the Iberian margin (9, 17–21) in the northeast North Atlantic Ocean (fig. S1). The North Atlantic is highly sensitive to terminations because of its role in the global conveyor belt of oceanic circulation and its proximity to Northern Hemisphere ice sheets (9). The Iberian

margin sediments preserve an excellent multiproxy paleoclimate record through T-II and the Last Interglacial (9, 17–21) (figs. S10 and S11). Our speleothem time series was assembled by using three stalagmites from Antro del Corchia, an Italian cave system that receives most of its recharge rainfall via westerly air masses crossing the North Atlantic (22). The stalagmite time series extends between ~120 and ~146 ka (Fig. 1) and is based on over 1400 oxygen isotope measurements fixed in absolute time by 56 mass spectrometric U-Th ages (tables S1 and S2 and figs. S3, S8, and S9).

The correspondence between Corchia $\delta^{18}\text{O}$ and Iberian-margin sea-surface temperatures (SSTs) through T-II (Fig. 2) is remarkable. Although the mechanisms that force speleothem $\delta^{18}\text{O}$ varia-

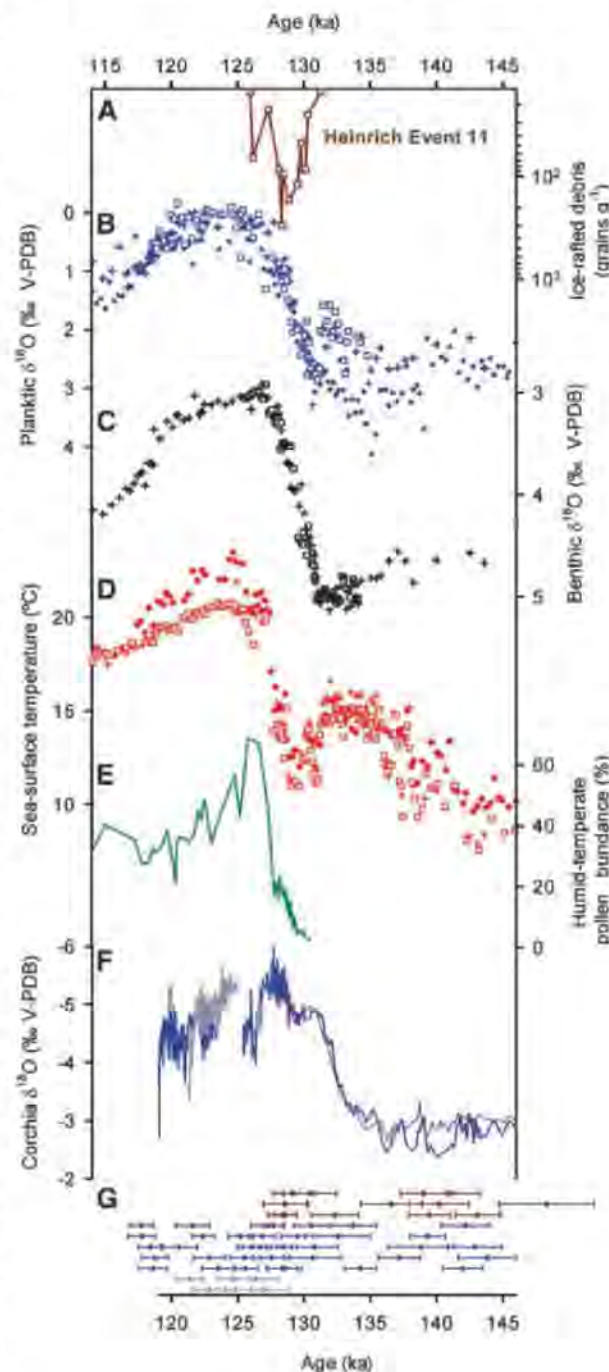


Fig. 1. Iberian-margin data from cores MD95-2042 [(20, 21) crosses], MD01-2444 [(9, 18) open squares], and ODP-977A [(17, 18) solid diamonds] placed on the ODP-977A time scale of (18) and the stacked Corchia speleothem $\delta^{18}\text{O}$ data. (A) Ice-rafted debris from MD01-2444 (9) (plotted on an inverted logarithmic scale). (B) Planktic foraminifera $\delta^{18}\text{O}$ (*Globigerina bulloides*) from MD95-2042 (20), MD01-2444 (9), and ODP-977A (17). (C) Benthic foraminifera $\delta^{18}\text{O}$ from MD95-2042 (20) (mixed species) and MD01-2444 (9) (*Globobulimina affinis*). (D) U^{37} alkenone-based SSTs from ODP-977A (17), MD01-2444 (18), and MD95-2042 (21). (E) Percentage abundance of warm humid-temperate pollen (Eurosiberian plus Mediterranean taxa) from MD95-2042 (20). (F) Corchia speleothem $\delta^{18}\text{O}$ profiles from stalagmites CC5 (blue), CC1 (maroon), and CC7 (gray). (G) Corchia speleothem radiometric ages with 95% error bars [same color scheme as in (F)].

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tions are complex (23), we believe that Corchia $\delta^{18}\text{O}$ is driven largely by variations in rainfall amount (22, 24) in response to changes in regional SSTs. Previous studies from Corchia show that speleothem $\delta^{18}\text{O}$ is sensitive to past changes in North Atlantic circulation at both orbital (22, 25) and millennial time scales (26), with $\delta^{18}\text{O}$ increasing during colder (glacial or stadial) phases and the reverse occurring during warmer (interglacial or interstadial) phases. During glacial/stadial periods, weaker North Atlantic meridional overturning circulation (MOC) results in a southward shift in the polar front (20), bringing cooler ocean waters into the middle latitudes, including the western Mediterranean Sea (27). The decline in regional air temperatures, evaporation, and moisture transport toward the Italian peninsula would lower the amount of rainfall reaching Corchia

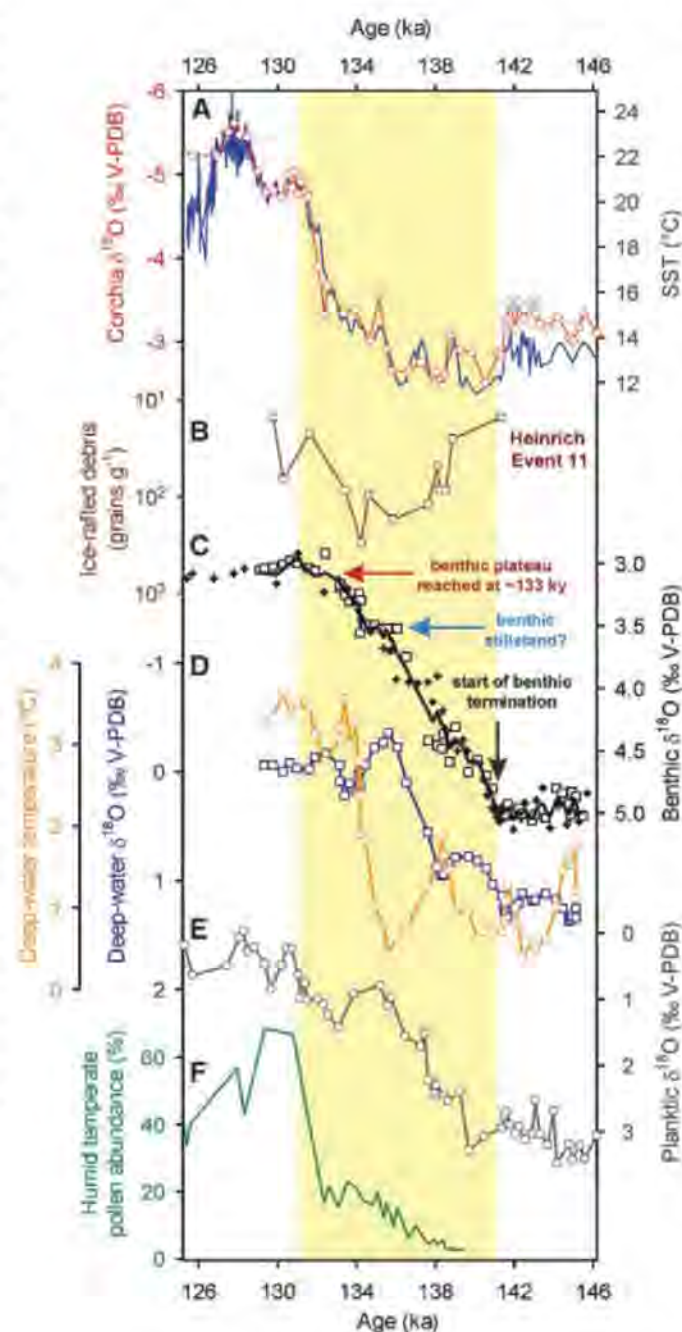
Cave, producing elevated stalagmite $\delta^{18}\text{O}$ values because of a reduction in the rainfall "amount effect" (24), a phenomenon well recognized in other Mediterranean speleothem records (28, 29). Under warm conditions, more intensive MOC increases regional SSTs and displaces the polar front retreats to higher latitudes. This favors increased air temperatures, evaporation, and moisture advection across the Mediterranean, generating higher rainfalls in the Corchia region and lower speleothem $\delta^{18}\text{O}$ values. Stronger MOC may contribute more isotopically depleted North Atlantic-sourced vapor compared with western Mediterranean-sourced vapor (30), further depressing the isotopic values during warm intervals. Although factors such as changes in surface ocean composition, cave and regional air temperatures, and the seasonality of rainfall would affect

speleothem $\delta^{18}\text{O}$ signatures through a termination (23), independent support for the forcing of Corchia $\delta^{18}\text{O}$ predominantly by rainfall amount is provided by trace element, initial uranium isotope ratio, and growth rate changes in these speleothems (figs. S4 to S7).

To investigate the Iberian marine sequence through T-II in more detail, we produced a multiproxy "Iberian-margin stack" on a common time scale by tuning the MD01-2444 (9, 18) and MD95-2042 (19–21) data to the ODP-977A chronology (17, 18) with use of the benthic and SST profiles (figs. S10 and S11). We then tuned the ODP-977A SST series to the precisely dated Corchia $\delta^{18}\text{O}$ series (Fig. 2A), enabling us to transfer the multiproxy Iberian-margin stack onto the Corchia radiometric time scale (Fig. 2, B to F, and fig. S12). The radiometrically tuned marine sequence through T-II shows that the monotonic decrease in $\delta^{18}\text{O}_b$ from cores MD01-2444 and MD95-2042 starts at 141 ± 2.5 ka (black arrow, Fig. 2C), heralding the commencement of the termination. It was demonstrated recently (9) that $\delta^{18}\text{O}_b$ from the Iberian margin during T-I and T-II were affected by changes in T_{dw} and $\delta^{18}\text{O}_{\text{dw}}$ because of variations in MOC and North Atlantic Deep Water (NADW) formation, thus corrupting the otherwise predominant ice-volume signature of $\delta^{18}\text{O}_b$. However, at the time of the initial $\delta^{18}\text{O}_b$ decrease these variations are negligible (Fig. 2D), indicating that $\delta^{18}\text{O}_b$ faithfully records the onset of deglaciation. Lastly, we constrain the timing of ice-rafted debris flux reaching the Iberian margin [and associated with Heinrich Event 11 (HI1) (31)] to between 140 ± 2.5 and 129 ± 1.5 ka (Fig. 2B).

SSTs experienced their first steady increase at 136 ± 2.5 ka (Fig. 2A), that is, at about the T-II midpoint. Together with the abrupt decrease in $\delta^{18}\text{O}_{\text{dw}}$ and increase in T_{dw} (Fig. 2D), this suggests a resumption of NADW formation at this time in response to a stronger MOC (14). The clear interruption to the monotonic decrease in Iberian $\delta^{18}\text{O}_b$ values between 136 and 134 ka (blue arrow, Fig. 2C) occurs about two-thirds of the way through the deglacial benthic shift, suggesting relatively high sea levels by this time. Concurrent increases in T_{dw} , $\delta^{18}\text{O}_{\text{dw}}$, and SSTs support intensified MOC (14), which runs counter to previous suggestions of substantially renewed ice-sheet growth and sea-level fall (32). The rise in SSTs is interrupted twice by pauses (~ 135 to 132.5 ka and ~ 131.5 to 129.5 ka), both of which are expressed in the Corchia $\delta^{18}\text{O}$ record (Fig. 2A). The oldest probably coincides with the post-Zeifen stadial (20), whereas the latter occurs just after the sharp rise in humid-temperate Euro-siberian and Mediterranean taxa that marks the start of the Eemian vegetation phase in southern Europe (20) (Fig. 2F). The close association between the abrupt SST rise off Iberia and increasing forest cover between these two pauses (~ 132.5 to 131.5 ka) is consistent with a recent age estimate of the abrupt postglacial increase in global CH_4 (131.2 ± 2 ka) (14).

Fig. 2. The Iberian-margin sequence from Fig. 1 replotted on the Corchia radiometric time scale by matching the $\delta^{18}\text{O}$ from stalagmite CC5 to the ODP-977A SST (23). (A) Overlay of Corchia $\delta^{18}\text{O}$ and ODP-977A SST (17) showing the close structural correspondence between the two records. The greater sampling resolution accounts in part for the higher variability in the stalagmite $\delta^{18}\text{O}$. (B) Ice-rafted debris (grains g^{-1}) from Heinrich Event 11 from MD01-2444 (9) (plotted on an inverted, logarithmic scale). (C) Benthic foraminifera $\delta^{18}\text{O}$ from MD01-2444 [open squares (9)] and MD95-02042 [crosses (20)]. (D) Deep-water temperature changes based on Mg/Ca ratios of benthic foraminifera (orange squares) and deep-water $\delta^{18}\text{O}$ variations (dark blue squares) through T-II from MD01-2444 [three-point smoothing, replotted from original data in (9)]. (E) Planktic foraminifera $\delta^{18}\text{O}$ from ODP-977A (17). (F) Percentage abundance of warm humid-temperate pollen (Euro-siberian and Mediterranean taxa) from MD95-2042 (20). The yellow section is the approximate period of T-II on the basis of the benthic $\delta^{18}\text{O}$.



Our results can be used to explore the phase relationships between sea level, $\delta^{18}\text{O}_b$, and the Last Interglacial SST optimum (14). During T-I, the "benthic plateau" (33) was attained by 10.1 ± 0.5 ka (34), when sea levels were ~ 40 m below present (40 mbsl) (35), and preceded the Holocene SST maximum off the Iberian margin (8 to 9 ka) by about 1 to 2 ky (17, 18) and the Holocene highstand (6.4 ± 1 ka) by 3.7 ± 1.1 ky (14). After T-II, SSTs off Iberia peaked between $\sim 129 \pm 1.5$ and $\sim 127 \pm 2$ ka (Fig. 2A) according to our record, ~ 4 ky after the start of our benthic plateau ($\sim 133 \pm 2$ ka; red arrow in Fig. 2C). This gives a SST–benthic plateau lag longer than that for T-I. As for the timing of the Last Interglacial sea-level highstand, age estimates based on coral U-series dating vary widely depending on whether open- or closed-system assumptions are used (15, 36). Such estimates must be regarded as minima given likely preservation biases resulting from erosion (16). The oldest reported closed-system age constraint from a tectonically stable margin placed the highstand onset at $\sim 129 \pm 1$ ka (36), yielding a benthic plateau–sea-level highstand lag almost identical to that of T-I (14), whereas a highstand age of 126 ± 1.7 ka has been determined from open-system–corrected coral ages (14, 15). A re-

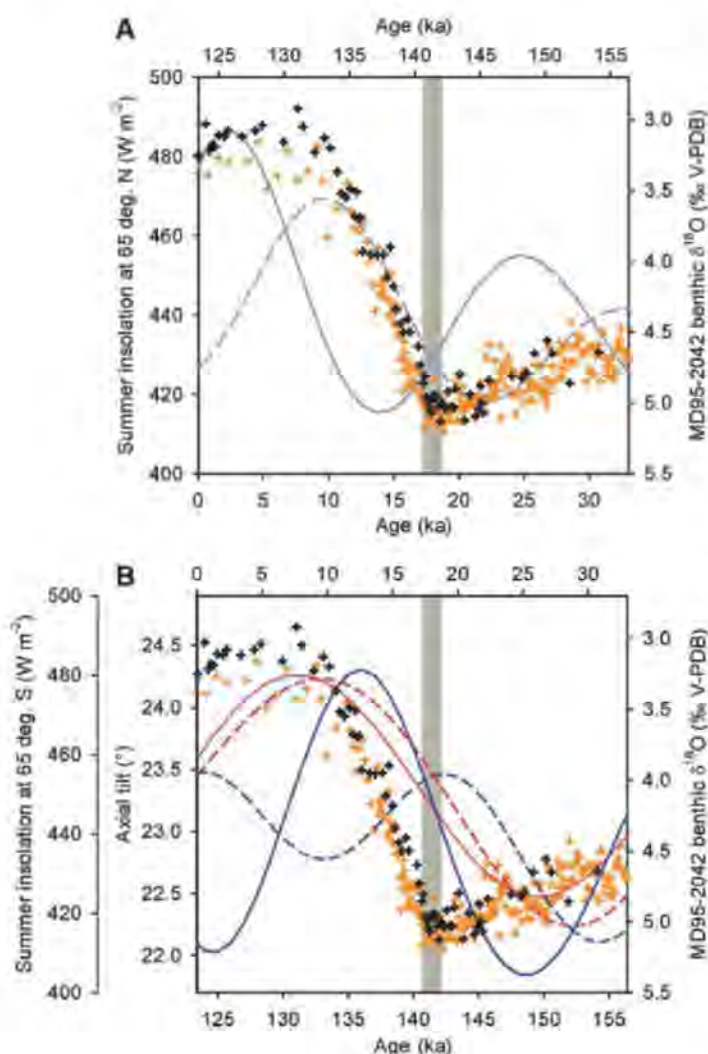
cent sea-level reconstruction for T-II (37) suggested a sea level of 30 mbsl at the time when the benthic plateau is reached, similar to that for T-I (40 mbsl) (14, 35). This reconstruction, which has been chronologically anchored in part by ~ 137 -ky-old corals that define a minimum age estimate for sea level at 85 mbsl, suggests a T-II starting point at ~ 141 ka (37). This is in excellent agreement with our revised benthic curve (Fig. 2C).

Our radiometric age–based benthic sequence provides a new opportunity to investigate orbital forcing and the timing of the last two glacial terminations. We compared the benthic record from MD95-2042 for T-I and T-II with changes in the intensity of high-latitude Northern and Southern Hemisphere summer insolation and Earth's obliquity (Fig. 3). We find that NHSI intensity is unlikely to be the driving force for T-II: Intensity values are close to minimum at the time of the start of T-II, and a lagged response to the previous insolation peak at ~ 148 ka is unlikely because of its low amplitude (Fig. 3A). This argues against the SPECMAP curve being a reliable age template through T-II, given the age offset of ~ 8 ky for the T-II midpoint (8) with respect to our record. A much stronger case can be made for obliquity as a forcing mechanism.

On the basis of our results (Fig. 3B), both T-I and T-II commence at the same phase of obliquity, and the period between them is exactly equivalent to three obliquity cycles (~ 123 ky). Obliquity is clearly very important during the Early Pleistocene (2, 38), and recently (4, 39) a compelling argument was advanced that Late Pleistocene terminations are also forced by obliquity but that they bridge multiple obliquity cycles. Under this model, predominantly obliquity-driven total summer energy is considered more important in forcing terminations than the classical precession-based peak summer insolation model, primarily because the length of summer decreases as the Earth moves closer to the Sun. Hence, increased insolation intensity resulting from precession is offset by the shorter summer duration, with virtually no net effect on total summer energy in the high latitudes (4, 39). By contrast, larger angles of Earth tilt lead to more positive degree days in both hemispheres at high latitudes, which can have a more profound effect on the total summer energy received and can act essentially independently from a given precession phase (4, 39). The effect of obliquity on total summer energy is more persistent at large tilt angles, lasting up to 10 ky (39), because of the relatively long period of obliquity. Lastly, in a given year the influence of maximum obliquity persists for the whole summer, whereas at maximum precession early summer positive insolation anomalies are cancelled out by late summer negative anomalies, limiting the effect of precession over the whole summer (39).

Although the precise three-cycle offset between T-I and T-II in our radiometric chronology and the phase relationships shown in Fig. 3 together argue strongly for obliquity forcing, the question remains whether obliquity changes alone are responsible. Recent work (40) invoked an "insolation-canon," whereby terminations are Southern Hemisphere–led but only triggered at times when insolation in both hemispheres is increasing simultaneously, with SHSI approaching maximum and NHSI just beyond a minimum. However, it is not clear that relatively low values of NHSI (at times of high SHSI) should play a role in deglaciation. An alternative is an insolation canon involving SHSI and obliquity. For T-I and T-II, the benthic $\delta^{18}\text{O}$ decrease commences when SHSI and obliquity reach similar values, with SHSI leading obliquity in both cases. During the two intervening obliquity cycles, SHSI lags obliquity. Thus, relatively high SHSI may instigate initial warming in the south. This may continue as the system approaches maximum obliquity, after which sustained and higher total summer energy occurs. The notion of Southern Hemisphere–led terminations is nothing new (41), but the mechanism or mechanisms that sustain this warming to the point where a termination is triggered have not previously been elucidated. A canon involving a lagging obliquity may well be the answer. Assembling similar records for earlier terminations will further test this model. Our study demonstrates

Fig. 3. Comparison between the benthic $\delta^{18}\text{O}$ record through T-I [orange crosses; plotted on the time scale of (21)] and T-II (black crosses; replotted on the Corchia time scale, this study) from core MD95-2042, showing similarity in the duration of both terminations and orbital parameters. (A) NHSI at 65°N (gray) for T-I (dashed line) and T-II (solid line). (B) SHSI at 65°S (blue) and obliquity curves (red) for T-I (dashed lines) and T-II (solid lines) and obliquity. The gray vertical bars linking the age axes mark the commencement points for both terminations and reveal that the age difference is equivalent to three obliquity cycles (~ 123 ky).



that precisely dated speleothems can play a key role in constraining the timing of earlier terminations, provided that close coupling with marine paleoclimate records can be demonstrated.

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Supporting Online Material

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Materials and Methods

Figs. S1 to S15

Tables S1 and S2

References

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Cellular Basis of Itch Sensation

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Itch and pain are two distinct sensations. Although our previous study suggested that gastrin-releasing peptide receptor (GRPR) is an itch-specific gene in the spinal cord, a long-standing question of whether there are separate neuronal pathways for itch and pain remains unsettled. We selectively ablated lamina I neurons expressing GRPR in the spinal cord of mice. These mice showed profound scratching deficits in response to all of the itching (pruritogenic) stimuli tested, irrespective of their histamine dependence. In contrast, pain behaviors were unaffected. Our data also suggest that GRPR⁺ neurons are different from the spinothalamic tract neurons that have been the focus of the debate. Together, the present study suggests that GRPR⁺ neurons constitute a long-sought labeled line for itch sensation in the spinal cord.

Itch has long been considered to be a submodality or subquality of pain (1–4), because the two sensations share many similarities (5). Whether itch and pain, two distinct sensations, are mediated by distinct neural circuits has been the subject of controversy (6–8). In the spinal cord, arguments for the “labeled line” came from electrophysiological recordings in cat showing the presence of a small subset of histamine-responsive, mechanically, thermally and mustard oil insensitive lamina I spinothalamic tract (STT) neurons (9). Recent studies in primates, however, found that all histamine-sensitive STT neurons were responsive to noxious mechanical and chemical

stimuli, notably capsaicin, arguing against the “labeled line” for itch (10, 11). Although our previous data suggested that gastrin-releasing peptide receptor (GRPR) is an itch-specific gene in the spinal cord (12), they could not be extrapolated to imply that GRPR⁺ neurons are itch specific, simply because neurons expressing one sensory modality-specific gene may also express other sensory modality-specific genes, as often seen in sensory neurons (13). One way to address this issue is to selectively ablate a subset of itch-signaling neurons and assess whether pain behaviors are altered in the absence of these neurons. We selectively ablated GRPR⁺ neurons in the spinal cord of mice by intrathecal administration of bombesin-saporin (bombesin-sap), a toxin coupled to bombesin that binds with high affinity to GRPR and results in GRPR internalization along with bombesin-sap and cell death (fig. S1) (14, 15).

We first determined the optimal dose and time course of bombesin-sap treatment. Intra-

thecal injection of bombesin-sap ablated GRPR⁺ neurons and reduced pruritogen-induced scratching behaviors in a dose-dependent manner (fig. S2). Most of GRPR⁺ neurons (>75%) were lost 2 weeks after single intrathecal injection of bombesin-sap (400 ng) (Fig. 1, A to C). To determine the specificity of bombesin-sap treatment, we analyzed several subpopulations of neurons in the spinal cord by using lamina-specific molecular markers. Expression of neuromedin U receptor 2 (NMUR2) and prodynorphin was not affected in lamina I of mice treated with bombesin-sap (Fig. 1, D to F, and fig. S3), nor was neurokinin 1 receptor (NK1) (Fig. 1, G to I), a lamina I and III gene expressed in a subset of neurons known for their involvement in nociceptive transmission (15, 16). Expression of lamina II markers such as neurotensin and PKCγ in the bombesin-sap group was also not affected (Fig. 1, J to O), nor was the projection of primary afferents (fig. S4). Saporin conjugated to a random peptide sequence (blank-sap) did not show cytotoxicity effects (figs. S4 and S5).

We next examined scratching behaviors of mice treated with bombesin-sap in response to intradermal injection of a panel of histamine-dependent pruritogenic agents. Unlike the control mice, which exhibited vigorous scratching response after intradermal injection of histamine, bombesin-sap-treated mice showed profound scratching deficits (reduced by 77%) (Fig. 2A). Scratching behaviors evoked by compound 48/80 (17) and serotonin [5-hydroxytryptamine (5-HT)] were also dramatically reduced relative to the control mice (by 79% and 88%, respectively) (Fig. 2, B and C, and fig. S9D). We further examined scratching behavior evoked by endothelin-1

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(ET-1), whose pruritogenic effect is partially dependent on histamine (18). Whereas ET-1 elicited robust scratching behavior, mice treated with bombesin-sap exhibited scarce scratching responses (reduced by 84%) (Fig. 2D).

We next evaluated scratching behavior elicited by two histamine-independent pruritogenic agents: an agonist of the protease-activated receptor 2 (PAR2) (19) and chloroquine that causes pruritus when used as an antimalaria drug in humans (20). Bombesin-sap-treated mice showed significantly reduced scratching responses compared with the control mice in both tests (reduced by 71% and 85%, respectively) (Fig. 2, E and F). To ascertain whether GRPR⁺ neurons are also important for chronic itch, for which no effective treatment is available (21, 22), we examined mice treated with diphenylcyclopropenone (DCP), a topical immunotherapy agent used in the treatment of alopecia areata that often results in severe side effects, including eczematous skin, contact dermatitis, and intense itching in both patients and mice (23, 24). Mice treated with DCP showed increased and persistent scratching behavior (Fig. 2G). In contrast, scratching responses of the bombesin-sap-treated mice to DCP were nearly lost (Fig. 2G), despite their normal motor function (fig. S6). The remarkable phenotype raises a question of whether certain subsets of non-GRPR⁺ neurons that may express other bombesin-like peptide receptors (14) might have also been ablated by bombesin-sap, thereby contributing to the loss of scratching response. Because our molecular analysis is constrained by a very limited number of lamina I-specific markers, it is likely that a loss of a small subset of non-GRPR⁺ neurons that are important for itch may have escaped detection. To examine this possibility, we compared scratching behaviors of GRPR mutant mice treated with bombesin-sap and with blank-sap and found that the two groups showed comparable scratching responses to a variety of pruritogenic agents (fig. S7), demonstrating that protecting GRPR⁺ neurons from being ablated by the GRPR mutation completely abolished the effect of bombesin-sap. Thus, even though some non-GRPR⁺ neurons that could also bind to bombesin-sap may have been lost, they are unlikely to be involved in itch signal transmission.

Although we have shown previously that GRPR is not important for nociceptive transmission, we have been unable to exclude the possibility that GRPR⁺ neurons are involved in pain (12). To test whether GRPR⁺ neurons are required for pain sensation, innocuous and noxious mechanical sensitivity of mice was examined by von Frey filaments and the Randall-Selitto test, and no significant differences were found between the two groups treated with bombesin-sap and blank-sap, respectively (Fig. 3, A and B). Acute thermal pain as assessed by the paw withdrawal (Hargreaves), water immersion, and hot plate tests also remained unaltered in the bombesin-sap group (Fig. 3, C to E). We further tested inflammatory

pain responses and found that licking and flinching behaviors elicited by intraplantar injection of 5% formalin in both phases were indistinguishable between the treated group and the control group (Fig. 3F). Mustard oil and capsaicin, which elicit a sensation of burning pain, also evoked comparable licking and flinching behaviors between groups (Fig. 3, G and H). Consistently, persistent inflammatory pain of longer duration was evaluated using Freund's complete adjuvant model, and no difference in mechanical hypersensitivity was found between groups (fig. S8A). Lastly, we asked whether there was an alteration of neuropathic pain in these mice using the partial sciatic nerve injury model, and mechanical allodynia in bombesin-sap-treated mice appeared normal (fig. S8B).

Our results are unexpected in several aspects. In marked contrast to the findings that the response of GRPR mutant mice to histamine-dependent pruritogenic stimuli was either not affected or modestly reduced (fig. S9, A to C) (12), bombesin-sap-treated mice showed nearly complete loss of scratching responses to both histamine-dependent and -independent pruritogenic stimuli, suggesting that GRPR⁺ neurons may contain a repertoire of itch-specific signaling molecules that are programmed differentially to transmit pruritogenic signals with distinct underlying mechanisms. Given recent identification of two separate itch pathways in STT neurons (11), it will be interesting to determine whether GRPR⁺ neurons comprise distinct subpopulations with discrete pruritic responsiveness. Another surprising finding is that several lines of evidence suggest that GRPR⁺ and

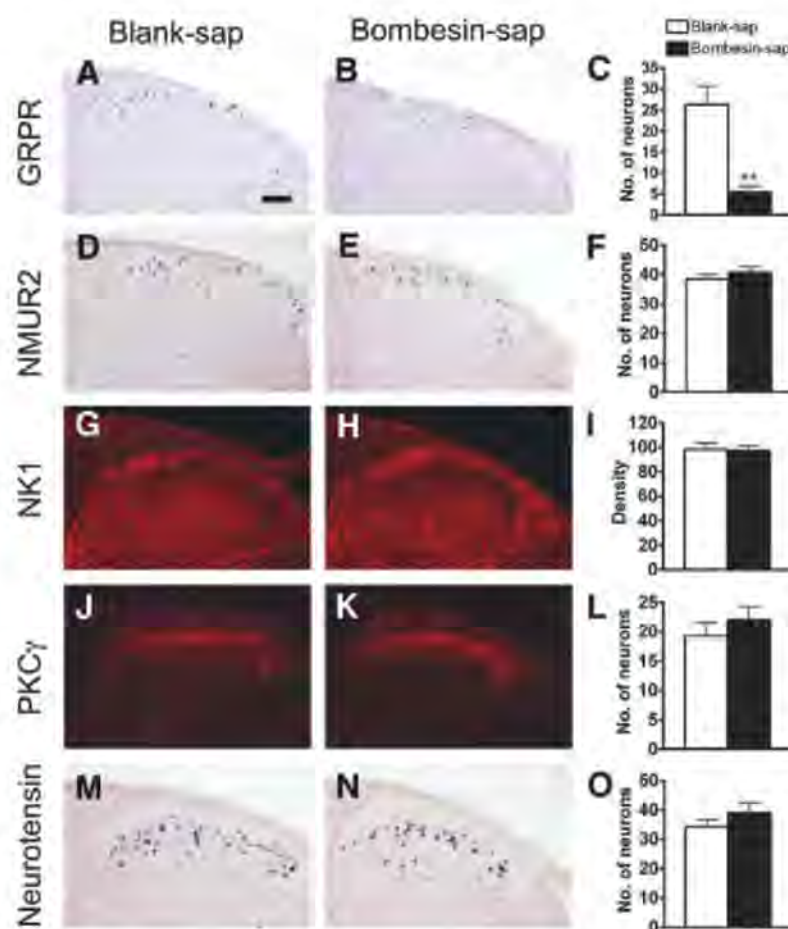
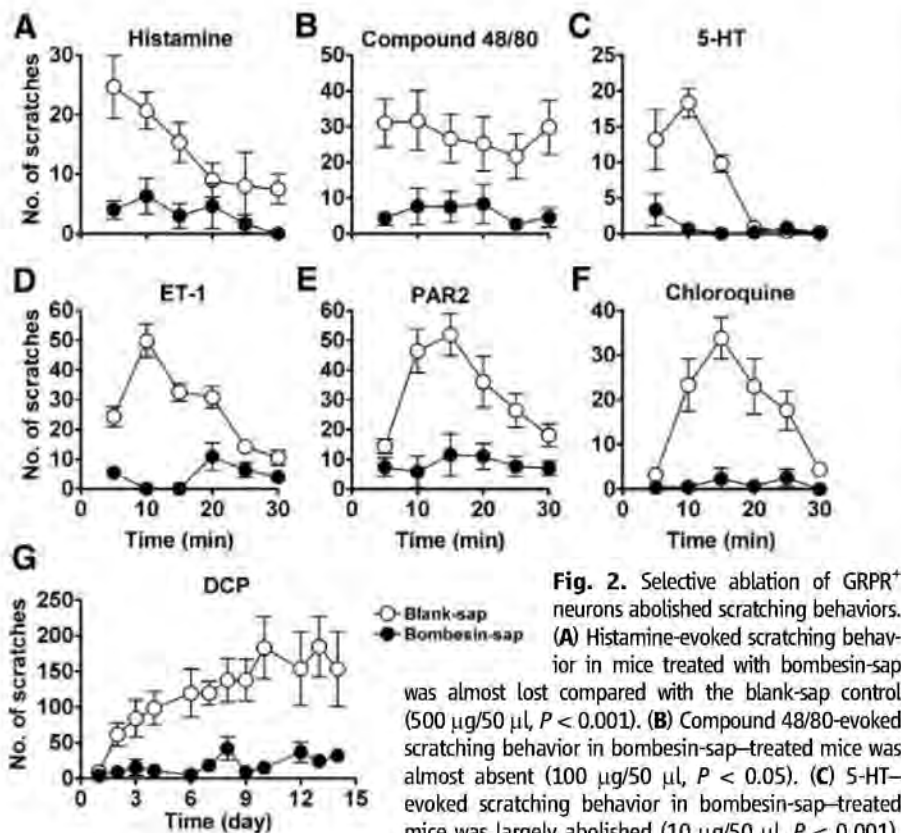


Fig. 1. Selective ablation of GRPR⁺ neurons in the spinal cord. Comparison of molecular expression [(C), (F), (I), (L), and (O); black bars, bombesin-sap group; white bars, blank-sap group] in the superficial spinal cord of mice treated with blank-sap [(A), (D), (G), (J), and (M)] and bombesin-sap [(B), (E), (H), (K), and (N)]. (A and B) GRPR expression in lamina I detected by in situ hybridization (ISH). (C) About 80% of GRPR⁺ neurons were lost in the bombesin-sap group compared with the blank-sap group (**P < 0.01). (D and E) NMUR2 expression in lamina I detected by ISH. (F) The number of NMUR2⁺ neurons was similar between the bombesin-sap and blank-sap groups (P > 0.05). (G and H) NK1 receptor expression in the dorsal spinal cord detected by immunocytochemistry. (I) The density of NK1 signal in lamina I was comparable between the bombesin-sap and blank-sap groups (P > 0.05). (J and K) PKCγ in lamina I layer detected by immunocytochemistry. (L) The number of PKCγ⁺ neurons was comparable between groups (P > 0.05). (M and N) Neurotensin expression in lamina II detected by ISH. (O) The number of neurotensin⁺ neurons was comparable between the bombesin-sap and blank-sap groups (P > 0.05). Scale bar, 100 μm. Student's *t* test. *n* = 4 to 6 mice for each group. Sap, saporin. Error bars, mean ± SEM.



bombesin-sap-treated mice was largely gone ($P < 0.001$). (E) The PAR2 agonist-evoked scratching behavior in bombesin-sap-treated mice was almost absent (SLIGRL-NH₂, 100 μ g/50 μ l, $P < 0.001$). (F) Chloroquine-evoked scratching behavior in bombesin-sap-treated mice was also absent (200 μ g/50 μ l, $P < 0.001$). (G) Scratching behavior evoked by DCP was nearly blocked in mice treated with bombesin-sap compared with blank-sap ($P < 0.001$). Two-way repeated measured analysis of variance (ANOVA). $n = 6$ to 9 mice for each group. Sap, saporin; ET-1, endothelin-1; PAR2, protease-activated receptor 2; DCP, diphenylcyclopropenone. Error bars, mean $\pm$ SEM.

STT neurons are two nonoverlapping subpopulations. First, expression of NK1, which is expressed in ~80% of STT neurons (25, 26), is normal in bombesin-sap-treated mice, and the ablation of NK1⁺ cells compromised chronic pain behaviors in rats (15, 16), whereas a loss of GRPR⁺ neurons did not. Second, a lesion of the STT pathway always impaired both itch and pain sensations (27, 28). Moreover, histamine- or cowhage-responsive STT neurons in primates also responded to capsaicin (10, 11). By contrast, our comprehensive pain behavioral analysis reveals that despite their critical roles in both acute and chronic itch, GRPR⁺ neurons are dispensable for both innocuous and noxious stimuli across a broad range of sensory modalities, notably including capsaicin-evoked behavior. Taken together, GRPR⁺ neurons represent a previously unrecognized subpopulation of lamina I neurons that confers the specificity of itch sensation. A detailed understanding of the anatomic basis of GRPR⁺ neurons (interneurons versus projection neurons) and their relationship with STT neurons will require further study. Nevertheless, our study supports the labeled line for itch in the spinal cord and provides an important cellular basis for explaining how a pruritogenic stimulus—received by cutaneous sensory receptors, conveyed by primary afferents, and discriminated and transmitted by the spinal cord—is ultimately perceived by the brain as a major sensation that is distinguishable from pain.

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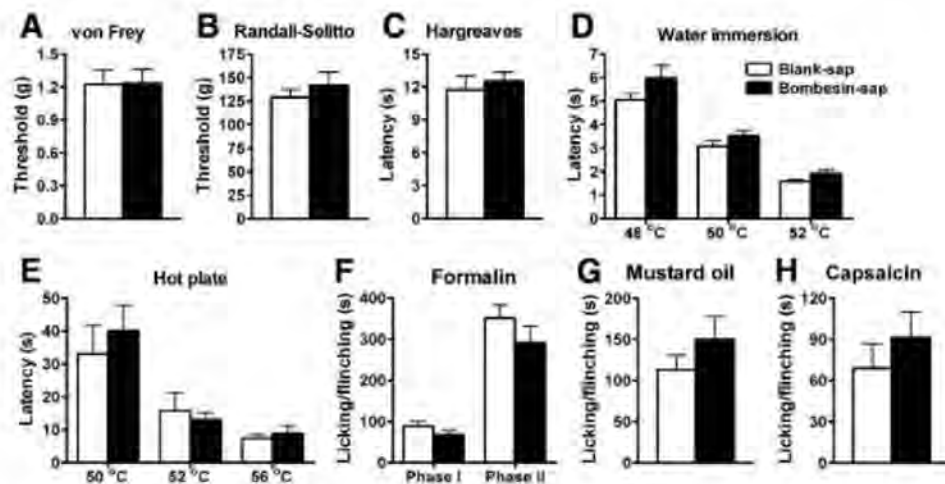


Fig. 3. Normal pain behaviors in mice treated with bombesin-sap. (A) Mechanical sensitivity in bombesin-sap-treated mice as measured by paw withdrawal threshold upon exposure to von Frey filaments was comparable to mice treated with blank-sap ($P > 0.05$). (B) The tail-flick latencies in the Randall-Selitto test did not show a significant difference between groups ($P > 0.05$). (C to E) Responses to noxious thermal stimulation measured by the paw withdrawal latency (Hargreaves) test (C), the water immersion latency test (D), and the hot plate test (E) were indistinguishable between groups ($P > 0.05$). (F) Spontaneous pain responses in the first (0 to 10 min) and second (10 to 60 min) phases of the formalin test were comparable between mice treated with blank-sap and bombesin-sap ($P > 0.05$). (G) Spontaneous pain response in mustard oil test was comparable between groups ($P > 0.05$). (H) Spontaneous pain response induced by intraplantar injection of capsaicin (0.1%) was comparable between groups ($P > 0.05$). Student's *t* test. $n = 6$ to 9 mice for each group. Sap, saporin. Black bars, bombesin-sap group; white bars, blank-sap group. Error bars, mean $\pm$ SEM.

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Supporting Online Material
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Materials and Methods

Figs. S1 to S9
References

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Attitudes and Action: Public Opinion and the Occurrence of International Terrorism

Alan B. Krueger^{1*†} and Jitka Malečková²

The predictors of terrorism are unclear. This paper examines the effect of public opinion in one country toward another country on the number of terrorist attacks perpetrated by people or groups from the former country against targets in the latter country. Public opinion was measured by the percentage of people in Middle Eastern and North African countries who disapprove of the leadership of nine world powers. Count models for 143 pairs of countries were used to estimate the effect of public opinion on terrorist incidents, controlling for other relevant variables and origin-country fixed effects. We found a greater incidence of international terrorism when people of one country disapprove of the leadership of another country.

Understanding the relationship between public attitudes and the occurrence of terrorism is important because although terrorist acts are rare, public opinion can provide an early warning signal and be an alternative indicator of terrorist threats. In addition, estimating the relationship between public opinion and acts of terrorism can help us understand the circumstances that lead to terrorism. For example, general disapproval of another country's leadership and policies could create a broader pool of people who provide material support for terrorist cells or join terrorist groups, resulting in more terrorist acts. Public opinion could also act as an incentive, providing a source of approval (or disapproval) encouraging (or discouraging) individuals to participate in terrorist activities. If public opinion toward another country is unrelated to the incidence of terrorism perpetrated against that country, there would be support for the view that terrorism is carried out by a fringe group with views and support networks that lie far from the mainstream of society.

With the exception of voting, little research has explored whether public attitudes translate into concrete actions (*1*). This paper addresses the question of whether there is a relationship between attitudes toward a foreign country, as ex-

pressed in public opinion polls on foreign leaders' performance, and the occurrence of terrorism against that country.

Specifically, we examined whether the public attitudes in country "i" toward the leadership of country "j" are related to the likelihood that people or groups from country i perpetrate terrorism against people or property from country j. We used data from the Gallup World Poll on the public opinion of residents in 19 Middle Eastern and North African countries (MENA, broadly defined) regarding the leaders of nine world powers (the United States, the United Kingdom, Russia, Germany, France, Canada, Japan, China, and India) in 2006 to 2007. This survey asked representative samples of the public in each country whether they approved or disapproved of the job performance of the leadership in the selected countries. Although the public opinion question was confined to the job performance of leaders of foreign countries, the Gallup data provide the broadest sample available. We link this information to the number of terrorist acts committed by people and groups from each of our sample of MENA countries against targets from each of the nine countries in 2004 to 2008 on the basis of data from the National Counter Terrorism Center (NCTC). We also statistically controlled for the effects of several other factors that may be related to terrorism, such as economic conditions, civil liberties, demographics, and the geographic distance between countries.

Public opinion toward other countries is potentially influenced by many factors, including historical animosities, religious rivalries, and economic competition, but our survey data refer specifically to country i's views of the job per-

formance of the leadership of country j. Although attitudes toward foreign leaders is not the only indicator of attitudes toward a country and its policy (*2*), the World Poll data should reflect the approval or disapproval of policies pursued by foreign governments and the general way in which the leadership of the country is perceived.

The Gallup World Poll has been conducted in more than 130 countries (*3*). We have obtained access to the micro survey data for 2006 and 2007 in order to compute statistics on public opinion concerning foreign countries. The specific question we used is, "Do you approve or disapprove of the job performance of the leadership of [named country]?" The named countries were the United States, the United Kingdom, Russia, Germany, France, Canada, Japan, China, and India, although Canada and India were not asked in all countries. These nine countries were selected by Gallup because they are world powers in terms of economic size, population, or military strength. About 1000 people were surveyed in each country per year, usually in face-to-face interviews. Samples were drawn to be nationally representative, and sample weights were provided to adjust for nonresponse disproportionalities. We calculated the (weighted) percentage of the population who disapproved of the job performance of each of the nine countries' leaders, which we refer to as the disapproval rate.

We focus on public opinion in 19 MENA countries because that is a region of great interest, with a wide range of variability in attitudes and terrorist incidents, and because of other data restrictions. Specifically, we have data on Afghanistan, Algeria, Cyprus, Egypt, Iran, Israel, Jordan, Kuwait, Lebanon, Mauritania, Morocco, Pakistan, Palestine, Saudi Arabia, Sudan, Tunisia, Turkey, the United Arab Emirates (UAE), and Yemen (table S1). We dropped Afghanistan from our regression analysis because gross domestic product (GDP) is not available for the country. Disapproval of the performance of foreign leadership varied considerably across the countries, from a disapproval rate of 13% (Morocco regarding Canada) to a high of 91 or 92% (UAE regarding the United States and Cyprus regarding the United States, respectively). There was also considerable variation within countries. For example, looking just at Saudi Arabians, the disapproval rate ranged from 34% concerning Japan to 88% concerning the United States. The United States and United Kingdom had the highest average disapproval rating across all countries (71% for both countries), whereas Japan had the lowest rating (41%).

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We collected data from NCTC's Worldwide Incidents Tracking System (WITS) on the number of terrorist incidents perpetrated by people or groups from each of the MENA countries that were directed against people or property from each of the nine powers from January 2004 to August 2008 (4). The WITS database is the most comprehensive source of information on international terrorist events that is publicly available. A terrorist attack is defined by the NCTC as an incident "in which sub-national or clandestine groups or individuals deliberately or recklessly attacked civilians or noncombatants."

Our analysis sample consisted of up to $18 \times 9 = 162$ country-by-country cells. For purposes of our analysis, we refer to the 18 MENA countries as the origin countries and the nine powers as the target countries, whether those countries were attacked intentionally or unintentionally. Because of missing data on public opinion (the omission of questions concerning Canada and India) in some origin countries, the sample was reduced to 144 cells. Restricting attention to these cells, there were 952 terrorist attacks in this period. However, 841 of these incidents were

perpetrated by groups from Pakistan against targets from India. The next highest number of incidents was 13 attacks carried out by Palestinians with victims from the United States. The Pakistan-India cell is clearly an outlying observation. Moreover, the fact that Pakistan and India share a border suggests that a different process could be at work for these two countries. Consequently, in most of our analysis we dropped the Pakistan-India pair, but our findings are similar if they are included. This left us with 143 country pairs. A total of 111 terrorist attacks were perpetrated by the origin countries against the target countries in this sample, involving 27 pairs (19%) of countries.

Other variables used in our analysis include average GDP per capita from 1997 to 2001, population and civil rights of origin and target countries, and percentage of Muslims of the population in the origin countries (5). In addition, we computed the distance between the capital cities of the origin and target countries. These variables have been identified as possibly related to the occurrence of terrorism in past research and hence are included as control variables in our analysis (6–13).

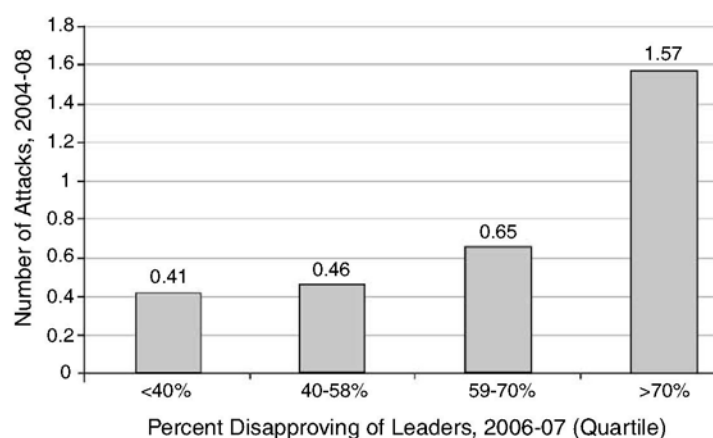


Fig. 1. Attitudes and international terrorist attacks. Shown are the numbers of attacks per pair of countries by public disapproval of foreign leaders. Calculations were made by the authors from Gallup World Poll data and NCTC WITS data.

Table 1. Negative binomial models to explain the number of terrorist incidents between origin and target countries. Sample size is 143 origin-by-target country cells. Mean (SD) of the dependent variable is 0.78 (1.90).

Explanatory variable	Mean (SD)	Coefficient estimate (SE)	
Disapproval rate	0.55 (0.20)	3.30 (1.67)*	3.00 (1.67)
Log distance†	1.15 (0.55)	−0.82 (0.25)*	−0.99 (0.37)
Origin log population	16.26 (1.42)	−0.14 (0.29)*	—
Origin civil liberties (inverse scale)	5.16 (1.38)	0.57 (0.29)*	—
Origin log GDP per capita	7.69 (1.26)	−0.11 (0.14)*	—
Origin proportion Muslim	0.84 (0.26)	−1.03 (1.10)*	—
Target log population	18.89 (1.12)	0.37 (0.20)*	0.55 (0.24)
Target civil liberties (inverse scale)	2.75 (1.68)	−0.12 (0.30)*	−0.21 (0.28)
Target log GDP per capita	9.23 (1.62)	0.41 (0.22)*	0.50 (0.24)
17 MENA country dummies		No	Yes
Pseudo R ²		0.13	0.25

*SE allows for correlated errors within origin countries.

†Distance is measured in thousands of miles.

If the country pairs are divided into quartiles based on the disapproval rate of the leadership of the nine powers by people in the MENA countries, the number of terrorist attacks arising from the MENA countries against people or property in the nine targets rises with disapproval (Fig. 1). The bivariate correlation between the number of attacks from country *i* against country *j* and the corresponding disapproval rate is 0.24 ($P < 0.01$).

To control for potentially confounding variables and to model the count nature of terrorist incidents, we estimated negative binomial regression models (Table 1). The general form of the models is

$$E(y_{ij}|\mathbf{x}) = \exp(x_{ij}\beta_1 + x_i\beta_i + x_j\beta_j) \quad (1)$$

where y_{ij} is the number of terrorist incidents perpetrated by people from country *i* on people or property of country *j*, $\mathbf{x}$ represents the explanatory variables (such as distance between countries and GDP per capita), *i* indexes the specific MENA country, and *j* indexes the target country. A negative binomial was selected to accommodate over dispersion of the dependent variable. We also estimated a fixed effects specification that includes dummy variables for each origin country in lieu of $x_i\beta_i$. Our inclusion of unrestricted origin-country dummies absorbs omitted variables, such as radical Islamic education, demographic differences, or male-female educational differences in the origin country, as long as those variables exert a constant effect across potential targets.

Consistent with findings of the past literature, terrorist incidents are less likely between pairs of countries that are separated by greater geographic distance (7). In addition, terrorism is unassociated with GDP per capita in the origin country but positively associated with GDP per capita in the target country and the degree of civil liberties in the target country.

We found a sizable and robust positive relationship between the number of terrorist incidents occurring from country *i* against country *j* and the rate at which people in country *i* disapprove of the job performance of country *j*'s leaders. A 20-percentage-point increase in the disapproval rate of a country's leaders, the equivalent of one SD in this sample, was associated with a 93% $\{100 \times [\exp(0.66) - 1]\}$ increase in the number of terrorist attacks ($P < 0.05$) (Table 1). The estimated magnitude of this effect was 82% if unrestricted country-of-origin dummies are included in the model ($P < 0.01$) (Table 1). The resilience of the effect of public disapproval to controlling for country-of-origin dummies suggests that omitted origin-country variables are not biasing the estimates, although it is possible that origin-country variables interact with specific targets and therefore are not fully absorbed by the country fixed effects.

We estimated several alternative models to explore the robustness of the effect of the

disapproval rate on the number of terrorist incidents [see the supporting online material (SOM) text for a full description]. No single origin country was responsible for the effect we found, and weighting the country-level observations to reflect the underlying Gallup sample sizes increased the magnitude of the effect. Although past studies have suggested that the “youth bulge” (the proportion of young people in the population) is an important determinant of terrorist activity (14, 15), the inclusion of the share of the population age 15 to 24 did not meaningfully affect our estimates.

Restricting our sample to the MENA region, where terrorism is relatively more common, could attenuate the correlation between public opinion and terrorist incidents. In future work, it would be useful to test whether public opinion has a similar relationship with terrorist incidents in a larger set of countries. Another issue concerns causality: Our data do not allow us to infer whether terrorists respond to public opinion per se or whether the political preferences of terrorists respond in the same way as those of the general public to external events. Moreover, it is not possible to draw inferences concerning individual motivations from regressions with aggregate data (16). Nevertheless, public opinion appears to provide a useful indicator of terrorist activity.

Assuming that the correlation between public opinion and terrorism is not a statistical artifact of omitted variables or reverse causality, greater disapproval of another country's leaders and policies could result in more terrorist incidents for at least two reasons. On one hand, it could increase the number of people in a society who provide material support and encouragement for terrorist cells (17). It is also plausible that international terrorism directed at country *j* is greeted with greater legitimacy as the level of disapproval toward country *j*'s leaders held by the median person in country *i* increases. On the other hand, a shift in public disapproval could increase the number of people willing to join terrorist cells and carry out terrorist acts themselves. In this case, the whole distribution of views—extremists as well as the median person—would shift as more people disapprove of another country. Of course, both of these effects could occur simultaneously, but understanding the mechanism by which public opinion relates to terrorism can inform counterterrorism policies. (see the SOM text for an elaboration of these cases.)

The Gallup survey data on the public's views toward the leadership of other countries do not allow us to distinguish between these two cases. Our measure reflects the median person's view but not the extent of extreme views. If future surveys collect information on the depth of disapproval toward country *j*, however, it would be possible to determine which part of the distribution of public opinion is related to terrorist incidents, the median or extreme tail. Distinguishing between these cases would help

inform counterterrorism strategies and should be a priority for future research.

Nevertheless, our results are inconsistent with one hypothesis, that public opinion is irrelevant for terrorism because terrorists are extremists who act independently of their countrymen's attitudes toward the leadership of the countries that they attack. To explore the reason why public opinion is correlated with terrorism further, it would be useful to collect additional data on public attitudes that probes the intensity of disapproval of foreign countries and assesses various dimensions of disapproval (such as leaders, policies, form of government, people, and so on).

Another extension of the analysis presented here would be to take advantage of changes in the leadership and policies of a country. For example, the election of Barack Obama—who opposed the war in Iraq, criticized the use of torture and detention of alleged terrorists at Guantanamo Bay, and offered to engage in “aggressive personal diplomacy” with leaders of Middle Eastern countries such as Iran—may well lead to a reduction in public disapproval toward the leadership of the United States in the MENA region. Will changes in terrorist activity accompany changes in public sentiment toward the United States, if public sentiment does indeed change? Relatedly, when longitudinal data become available, researchers will be able to examine more systematically the potential role of reverse causality, that is, whether attacks by terrorists from country *i* on country *j* cause citizens in country *i* to downgrade their approval of the leadership of country *j*.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/325/5947/1534/DC1

SOM Text

Figs. S1 and S2

Table S1

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Highly Variable Spread Rates in Replicated Biological Invasions: Fundamental Limits to Predictability

Brett A. Melbourne^{1*} and Alan Hastings²

Although mean rates of spread for invasive species have been intensively studied, variance in spread rates has been neglected. Variance in spread rates can be driven exogenously by environmental variability or endogenously by demographic or genetic stochasticity in reproduction, survival, and dispersal. Endogenous variability is likely to be important in spread but has not been studied empirically. We show that endogenously generated variance in spread rates is remarkably high between replicated invasions of the flour beetle *Tribolium castaneum* in laboratory microcosms. The observed variation between replicate invasions cannot be explained by demographic stochasticity alone, which indicates inherent limitations to predictability in even the simplest ecological settings.

Spatial spread has been the subject of intense study by ecologists (1), beginning with classic cases like introduced muskrats in Europe and oaks in the United Kingdom (2). This

work has provided the basis for attempts to control invasive species ranging from zebra mussels to many agricultural pests (3). In all cases, prediction of spread rates is a key question. There

are two fundamental ways of predicting spread (1), on the basis of either estimating parameters in a model (4, 5) or extrapolating from initial observations of spread or spread in another location (6). In both cases, obviously, questions of uncertainty or randomness are key aspects of prediction. These questions of the role of uncertainty in ecological systems and its implication for prediction are of fundamental importance not only for the specific case of spatial spread, but for more general issues of management (7, 8). By focusing on the role of uncertainty in understanding spatial spread, we obtain insights into general questions of importance for management of ecological systems.

Stochastic models are needed to assess uncertainty in the rate of spread because traditional deterministic models provide no information about variance. Analyses have shown that linear stochastic models have the same rate of spread as the equivalent deterministic model, whereas stochasticity slows spread in nonlinear (density-dependent) models (9, 10). Investigations of the variance of spread rate have largely relied on numerical simulations and suggest that variance between realizations can be high, especially when birth rates are low, variation in birth rates between individuals is high, or dispersal includes infrequent long-distance events (11–15). This work suggests that great uncertainty in an invasion forecast can be expected because of inherent biological variability.

Empirical documentation of variance in the rate of spread is scarce, hampered by the difficulty of replicating an invasion: Any invasion in nature is only one replicate, or realization, of the stochastic process. Some insights can be gained from natural pseudoreplicates in space or time. For example, many studies have found considerable variance in the rate of spread in different directions from a single point of release, such as for rabies or muskrats (4, 16). Similarly, childhood diseases such as measles show much variation in the rate of spread between successive outbreaks in the same location (17). However, in purely observational cases such as these, it is problematic to determine whether variance in spread rate is driven by inherent biological stochasticity or instead exogenously, such as by environmental factors that differ between the pseudoreplicates. To properly document variance due to biological processes, replicates need to experience identical external conditions. Tantalizing results from experimental epidemics of a fungal disease on radish seedlings in replicated laboratory microcosms suggest that variance in spread rate driven by biological stochasticity can be high (18, 19), although in these experiments replication was low and systematic differences between replicates oc-

curred and were important despite tight control of the ambient environment (13).

We studied variance in spatial spread in highly replicated experimental microcosms (20) using the red flour beetle, *Tribolium castaneum*. Each microcosm was a one-dimensional landscape consisting of discrete habitat patches linked together by holes drilled into the sides of adjacent patches. We introduced beetles to one end of the landscape and documented spread over multiple nonoverlapping generations with discrete growth and dispersal phases. This is an ideal system for studying variance in spread. First, the *Tribolium* model system has a long history in ecology, so the processes underlying growth and dispersal are well understood, mathematical models are well developed, and experimental protocols are well established (21–26). Second, conditions are tightly controlled in environmental chambers; this constraint minimizes the effect of external (environmental) factors and isolates the effect of biological stochasticity on the variance between replicates. Third, populations were censused completely, with negligible measurement error, which allowed us to investigate demographic stochasticity (23). Finally, both types of prediction can be done. We either forecast by using independent estimates of model parameters from separate experiments to establish growth and dispersal parameters, or by extrapolation from either the initial data from a particular experimental landscape or another experimental landscape.

We collected data for 30 replicate landscapes, composed of identical patches with standard medium, maintained under identical environmental conditions, and inoculated with 20 adult *T. castaneum* from the same stock culture. Even though the landscapes were putatively identical replicates, there was considerable variance in the distance spread among landscapes (Fig. 1). Furthermore, there was considerable variance in the spatiotemporal dynamics of abundance among landscapes (Fig. 2 and movie S1). We found that the variance, and hence uncertainty, in the distance spread increased with time (Fig. 3): By the end of the 13-generation experiment, the distance spread ranged from 10 to 31 patches, a threefold difference (Fig. 1). This demonstrates that intrinsic biological variability makes an extremely

large contribution to the variance in spatial spread. We next examine the consequences of this intrinsic variability for the uncertainty in ecological forecasts using different approaches to prediction.

One approach to ecological forecasting often applied to spatial spread is to estimate the parameters of population models using demographic observations separate from the dynamical (or spread) data, for example, observations of births, survival frequencies, and dispersal distances from mark-recapture studies (4, 5). To emulate this approach, we first derived models for the *Tribolium* microcosms and estimated parameters in independent experiments.

Spread models generally consist of two submodel components: local population growth and dispersal (1). We previously derived models for within-patch population growth, which comprehensively account for sources of stochasticity in the life cycle, including demographic stochasticity (in births, density-dependent mortality, and density-independent mortality), environmental stochasticity (variation in the growth rate between patches and in time), demographic heterogeneity (variation in the birth rate between individuals within a patch), and stochasticity in the sex of offspring (27). Biological and stochastic parameters of these models were estimated by using data from a growth experiment and show that demographic sources of stochasticity make an important contribution to variance in the number of offspring in the next generation (27).

Here, we derive models for dispersal that are closely matched to the experimental system (20). These include a standard discrete space diffusion model and variants allowing for stochasticity in dispersal rates between pairs of patches and between individual beetles, the latter giving rise to dispersal kernels with “fatter tails.” We fitted the dispersal models to data from a replicated dispersal experiment (20). These results show that variation in dispersal rates between pairs of patches was important, which enhanced dispersal variability, whereas there was little evidence for an important role of between-individual variability in dispersal rates (table S1, fig. S1).

We used the full stochastic spatial model, combining the best-fitting, independently estimated growth and dispersal submodels, to fore-

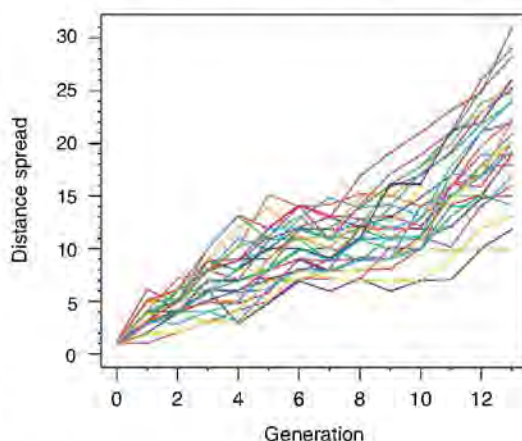


Fig. 1. Spatial spread of *T. castaneum* in 30 replicate landscapes through 13 generations. Landscapes were started with 20 adult beetles in patch 1, the leftmost end of the landscape. Distance spread is the number of patches spanning from (and including) patch 1 to the farthest forward occupied patch. Points on the y axis are perturbed slightly from integer values to see overlapping points.

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Fig. 2. Spatiotemporal dynamics of abundance and spatial spread of *T. castaneum* in 30 replicate landscapes. Each panel is a separate landscape. Landscapes were started with 20 adult beetles in patch 1, the leftmost end of the landscape. Patches are numbered from 1 (leftmost) to 31 (rightmost). Lines show the dynamics of the advancing invasion front, moving from left to right through 13 generations, and show the number of beetles in each patch in each generation. The red line is the final state of the invasion front (generation 13). A time-series animation of these data is available in movie S1.

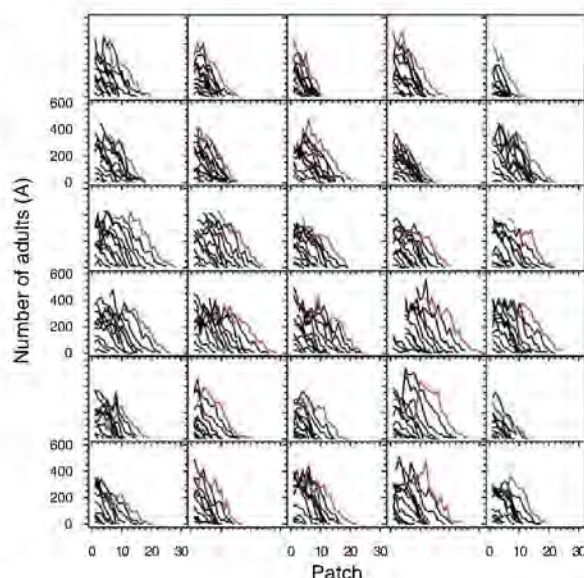
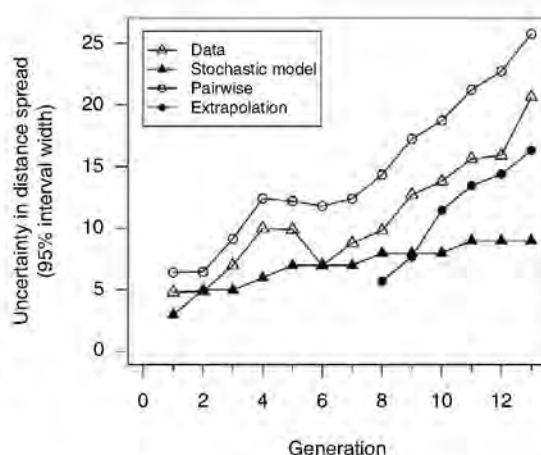


Fig. 3. Uncertainty in distance spread for the ensemble of replicate landscapes and for different forecast methods. Uncertainty was measured as the 95% interval width, calculated as the difference between the 2.5% and 97.5% quantiles. (**Key**) Data, the experimental data. Stochastic model, parameterized using independent experimental data on growth and dispersal. Pairwise, extrapolation from one landscape to another; interval width is for the prediction residuals (see fig. S5). Extrapolation, linear extrapolation from the first seven generations; interval width is for the prediction residuals (see fig. S4).



cast population spread. This standard approach to ecological forecasting slightly overestimated the mean rate of spread observed in the data but, more important, dramatically underestimated the variance in spread rate among landscapes (Fig. 3 and fig. S2). This is surprising, as the model was designed to be comprehensive in accounting for sources of stochasticity. Thus, the experimental data suggest that an important source of stochasticity is missing from the standard spread models.

The second approach to forecasting is extrapolating from initial observations of spread, or more generally from observations at another time or place. Apart from some special cases, such as Allee effects (28) and fat-tailed dispersal kernels (29), most biological scenarios lead to a linear increase in the distance spread (30). For each experimental landscape, we fitted a linear regression model for the first 7 generations to forecast the distance spread in generations 8 to 13. This approach seriously underestimated the uncertainty in the forecasts: The observed trajectories of many experimental landscapes exceeded the 95% prediction interval (fig. S3). In contrast to the naïve regression estimates of uncertainty, the forecast error directly measured from the ensemble of ex-

perimental landscapes was very high (Fig. 3 and fig. S4). By generation 13, the 95% interval width was 16, which is three-quarters of the ensemble mean distance spread (Fig. 3). Even higher forecast error was observed when the estimated spread rate from one landscape was used to predict the distance spread in another (Fig. 3 and fig. S5). Clearly, forecast uncertainty due to biologically generated variability is remarkably high, and it was only possible to measure this with replicated experimental invasions.

What, then, is the source of the unaccounted for and biologically generated variance in spread rates? The extra variability observed in the experimental ensemble might be accounted for by systematic biological differences between landscapes, such as those caused by founder effects. A hierarchical model fitted to the full spatiotemporal abundance data from the spread experiment (20) suggests that systematic variation in growth, cannibalism, and dispersal between landscapes was moderately high (Table 1). The hypothesis that all landscapes had the same (or similar) growth, cannibalism, and dispersal rates was rejected, because lower 95% confidence limits for the variation parameters (σ_R , σ_α , σ_D) were above zero (Table 1). This variation is unlikely to have been

Table 1. Fit of spatiotemporal model to test founder-effect hypothesis. The estimated parameters were $\bar{R}$, $\bar{\alpha}$, and $\bar{D}$, respectively, the mean density-independent per capita growth rate (per 48 hours), mean density-dependent parameter, and mean diffusion rate among landscapes; σ_R , σ_α , and σ_D , respectively, the standard deviation of R , α , and D among landscapes; k_{NB} , the dispersion parameter of the negative binomial distribution. Confidence intervals were obtained from quantiles of the posterior simulations.

Parameter	Estimate	95% CI
$\bar{R}$	2.54	2.43, 2.66
$\bar{\alpha}$	3.37	3.09, 3.67
$\bar{D}$ (48 h) ⁻¹	1.33	1.11, 1.55
σ_R	0.192	0.087, 0.348
σ_α	0.335	0.146, 0.589
σ_D (48 h) ⁻¹	0.550	0.415, 0.734
k_{NB}	2.03	1.94, 2.15

caused by external factors, such as environmental differences between landscapes, because these were tightly controlled. One explanation is that the random draw of the small founding population (20 individuals) from the stock beetle culture resulted in essentially different and randomly determined initial conditions for each landscape. Although further experimental work is needed to verify these model-based conclusions, variability in founders is clearly relevant not just to our experiments, but to almost all natural introductions as well, especially those repeated or where spread is driven by long-range dispersal and establishment of small outlying populations (14, 31).

Our results show that understanding and predicting spatial spread, as well as prediction in ecology more generally, must take into account considerable uncertainties. Prediction in ecology is becoming increasingly important, partly because of anthropogenic changes (8). Using insights only possible from replicated experiments under controlled conditions, we have suggested that even without exogenous sources of variability, fundamental uncertainties arise on account of inherent differences among individuals and small population sizes. These issues are ones that are central to questions of spread, more generally to invasive species or range shifts under environmental change, and still more generally to ecological prediction. Given the need for prediction both as a tool for ecological understanding and in public-policy decisions and management, it is important to understand both the magnitude and cause of uncertainty. These uncertainties are large, but our work here and by others (11, 13, 32) provides ways to estimate the magnitude of these uncertainties, which allows for estimates of errors in prediction.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/325/5947/1536/DC1

Materials and Methods

SOM Text

Figs S1 to S6

Table S1

References

Movie S1

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Controls on Diatom Biogeography in the Ocean

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The extent to which the spatial distribution of marine planktonic microbes is controlled by local environmental selection or dispersal is poorly understood. Our ability to separate the effects of these two biogeographic controls is limited by the enormous environmental variability both in space and through time. To circumvent this limitation, we analyzed fossil diatom assemblages over the past ~1.5 million years from the world oceans and show that these eukaryotic microbes are not limited by dispersal. The lack of dispersal limitation in marine diatoms suggests that the biodiversity at the microbial level fundamentally differs from that of macroscopic animals and plants for which geographic isolation is a common component of speciation.

Unlike terrestrial ecosystems, the oceans are an interconnected geophysical fluid that potentially allows planktonic organisms to disperse globally. Owing to their dispersal ability, microbial species exhibit a broad spatial distribution, which has led to the hypothesis that, below 1 mm body size, “everything is everywhere, but the environment selects” (1–3). However, several studies have questioned this idea, arguing that, like macroscopic animals and plants, microorganisms can exhibit biogeographic patterns and macroevolutionary trajectories linked not only to present-day environmental conditions but also to historical contingency and dispersal limitations (4–7). If marine planktonic microbes were limited by dispersal, the spatial range of species’ distributions should be constrained to a geographic area near the center of their origin, and, therefore, the degree of community similarity should gradually

decay with geographic distance (8, 9). However, because geographic distance is often correlated with specific environmental characteristics, disentangling the relative influence of these two factors on community divergence represents a major challenge in elucidating whether or not marine planktonic microbes are limited by dispersal (6, 10).

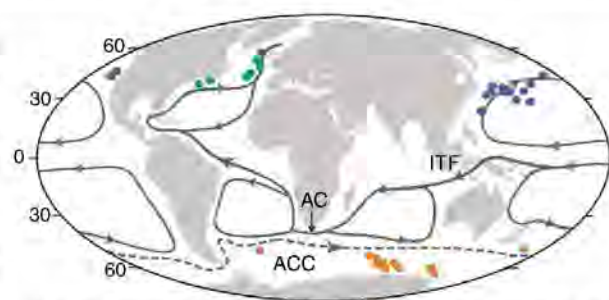
Using fossil diatom assemblages from far distant regions and contrasting open ocean environments, we tested the importance of environmental selection and dispersal limitation on the spatial distribution of marine diatom morphospecies. Owing to the relatively similar physicochemical

conditions between sites very far apart in the ocean, our analysis represents an ideal study case. Furthermore, the fossil record provides a time-averaged view of the effect of environment on past biological communities, reducing the range of extrinsic environmental variables that must be considered as causative factors.

Fossil assemblages of marine diatoms were extracted from the Neptune database, a global record of microfossil occurrences reported by the Deep Sea Drilling Project and Ocean Drilling Program (11). Our complete data set consisted of 225 assemblages containing 307 morphologically defined species (70 genera) from the early Pleistocene [~1.5 million years ago (Ma)] to the present (table S1). The analysis included assemblages typical of north temperate habitats from the Atlantic and Pacific Oceans, and high-latitude environments in the Southern Ocean from the Atlantic, Pacific, and Indian sectors and Antarctic waters (Fig. 1).

On time scales encompassing speciation, adaptive radiation, and long-term regime shifts such as historical climate change, the temporal turnover of community composition may bias our analysis, making it difficult to find biogeographical patterns. To set up the time scale of the analysis, we first quantified the change in floristic composition of diatom assemblages through time using the Jaccard index, a measure of similarity

Fig. 1. Paleogeographic reconstruction for Early Pleistocene (~1.8 Ma) showing locations of Deep Sea Drilling Project and Ocean Drilling Program sites used in this study. The pattern of major surface water current systems is shown schematically. The most likely dispersal routes between northern temperate habitats in the Atlantic and Pacific Oceans are (i) via the Indonesian through-flow (ITF) and Agulhas current (AC), (ii) a route to the North through the Arctic Ocean, or (iii) a route to the South within the Antarctic circumpolar current (ACC). Color code denotes different oceanic regions. These patterns of water mass circulation have persisted, albeit with substantial regional variations during the period of study. The figure is modified from Sexton and Norris (19).



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that emphasizes compositional changes (Fig. 2 and table S2) (12). The results reveal a slow and gradual decay of community similarity over the past 1.5 million years (My) of Earth's history (Fig. 2 and table S2). The pattern is consistent throughout the oceanic regions considered in the analysis. Using these data, we estimate a turnover time for these communities in the range of 2 to 8 My. For the purpose of our analysis, a time frame spanning 0.5 My satisfied the assumption of contemporaneity, that is, less than 15% reduction in community similarity.

For each time interval defined, the fossil assemblages were plotted simultaneously in a two-dimensional space according to their floristic similarity, using nonmetric multidimensional scaling (Fig. 3A and fig. S1). The analysis reveals a clear biogeographic differentiation between communities occupying temperate regions in the Northern Hemisphere and high-latitude environments in the Southern Ocean from the Atlantic, Indian, and Pacific sectors, and Antarctic waters; these communities share very few common species (Fig. 3B). In contrast, despite geographic/oceanographic barriers to dispersal, changes in community composition through time, and the disparity of data sources, far distant communities in north temperate regions of the Atlantic and Pacific Oceans exhibit remarkable similarities (Fig. 3B). Closer inspection of our database shows that, excluding poorly represented species (i.e., less than five occurrences in the global database), these oceanic regions respectively share ~95% and 75% of their total species pool.

Our sampling strategy allows comparison across large differences in longitude, separated by continents, and between large gradients in latitude with no land masses hindering dispersal. We assume that, to first order, the northern temperate habitats of the Atlantic and Pacific Oceans have been characterized by comparable environmental conditions over the past 1.5 My. In contrast, there are clear environmental differences between northern temperate habitats and the Southern Ocean sites considered in this analysis (13). At latitudes higher than ~45°S, the contemporary Southern Ocean is dominated by cold and nutrient-rich water masses comprising the Antarctic circumpolar current, which is delimited on its northern flank by the sub-Antarctic polar front (Fig. 1). In contrast to their northern hemispheric counterparts, where phytoplankton growth primarily is limited by nitrate, this oceanic region is characterized by strong iron limitation. Iron is an essential component of photosystems, and its limitation has been shown to influence the distribution of marine diatom species (14).

The proximity in the ordination space of fossil assemblages associated with northern temperate environments in the Atlantic and Pacific Oceans, and their separation from the Southern Ocean communities (Fig. 3), indicates that environmental conditions primarily control the global biogeography of marine diatom assemblages. These results, however, do not exclude spatial constraints

such as the geographic configuration of continents as relevant controls on species distribution. To further constrain the importance of geographic distance and dispersal limitations, we compared the differences in floristic composition within and between different oceanic regions. Here, our hypothesis presumes that the effect of dispersal limitation increases with geographic distance; that is, community dissimilarities should progressively increase from regional to global data sets. However, the analysis reveals that the taxonomic differences between far distant assemblages from north temperate regions in the Atlantic and Pacific Oceans are not significantly different from those observed within each oceanic region/basin (Fig. 3B).

Studies in freshwater ecosystems have demonstrated that geographical factors such as the fractal-like nature of drainage basins, the distance between lakes, or the availability of habitat primarily control the regional- to global-scale biogeography of diatom morphospecies (7, 15, 16). However, unlike freshwater ecosystems such as rivers and lakes, where the distribution of species is strongly constrained by habitat connectivity, the mutual contiguity of oceanic water masses

appears to be an effective conduit for global dispersal of marine planktonic microbes over evolutionary time (17–19). Far from the long-standing view that open ocean habitats are stable and uniform, mesoscale and submesoscale mixing processes, which are a highly important mode of energy dissipation in open ocean (20), mediate the intrusion of nutrient-rich deep waters into the euphotic zone and, hence, contribute to the widespread dispersal of marine planktonic diatoms. Furthermore, the circulation of surface ocean water masses and the strength of oceanic fronts may change in response to medium/long-term climatic variations, seasonal cycles, and transient events such as storms, temporarily opening alternative routes to seed dispersal.

Increasing evidence indicates that marine diatom morphotypes may be composed of several genetically distinct "cryptic" species characterized by subtle morphological differences (21, 22). This represents a potential caveat of our study, which is based on species defined by obvious morphological criteria. However, if dispersal overwhelmed the biogeographic effects of genetic divergence between populations, we would expect to find similar distribution patterns regard-

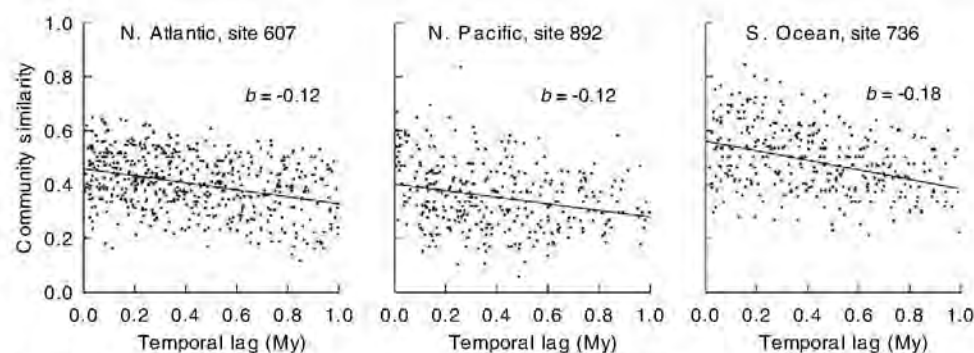
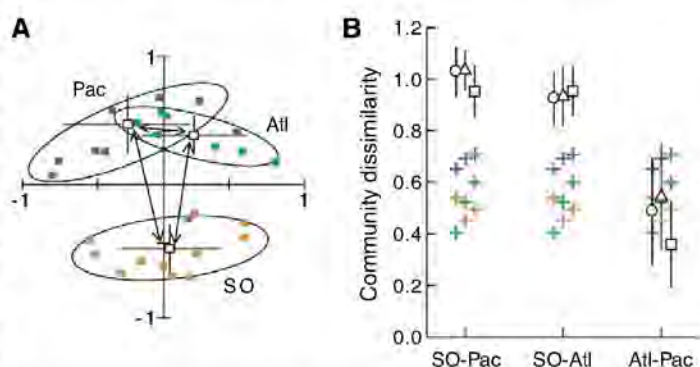


Fig. 2. Temporal decay of community similarity through the Pleistocene. Each point represents a single pairwise comparison between fossil diatom assemblages separated in time. The maximum temporal lag considered here is 1 My. b is the slope of the ordinary least square linear regression model. The plots are for different sites in the North Atlantic, North Pacific, and Southern Ocean (see also table S2).

Fig. 3. Inter- and intra-oceanic differences in community composition. (A) Representative illustration of floristic relationships among oceanic regions obtained by using nonmetric multidimensional scaling. Orange, blue, and green symbols are for Southern Ocean, North Pacific, and North Atlantic, respectively. Open squares are the mean coordinates in the ordination diagram for each oceanic region. Error bars represent ± 1 SD. The Euclidean distance between data points is an estimate of community dissimilarity (i.e., the longer the arrow, the larger the difference between communities). (B) Mean (± 1 SD) community dissimilarities between oceanic regions. Circles, triangles, and squares are different geological time intervals analyzed; 0 to 0.5, 0.5 to 1, and 1 to 1.5 Ma, respectively. Color crosses are mean community dissimilarities within each oceanic basin. Inter- and intra-oceanic mean community dissimilarities were estimated using a Monte Carlo simulation model (100 trials of the multidimensional scaling) and randomized combinations of among 15 to 50 communities (see also fig. S1).



less of the level of taxonomic resolution. In this regard, genetic analyses have shown the existence of widespread, although disjunct, distribution patterns for several cryptic species of the marine diatom *Skeletonema* (23). Similar results have been reported for other microbial plankton groups, such as picoeukaryote algae and foraminifera (17, 24). Alternatively, our results could reflect the convergence or parallelism of morphological traits among genetically unrelated taxa in disjunct oceanic regions.

Despite enormous environmental variability linked to glacial-interglacial climates of the Pleistocene, our analysis reveals that marine diatom communities have evolved slowly through gradual changes over the past 1.5 My of Earth's history (Fig. 2 and table S2). These patterns of community stability for extensive periods of geological time are probably associated with the great dispersal ability of marine diatoms (25, 26) and highlight the potential of microbial plankton communities for recovering from past and future climatic variations. This conclusion implies that there are few or no biogeographical traces of historical climate change in contemporary communities of marine diatoms.

Models of evolution of species commonly assume that tectonic barriers and water mass fronts act as effective isolating mechanisms (9). This is a necessary condition that precedes the delineation of biogeographic provinces sensu stricto (6, 9) and controls the development of global species richness. Our analysis, however, indicates that, even at the largest spatial scale, the geographic distribution of marine planktonic diatoms does

not seem to be limited by dispersal. These results, together with recent genetic evidence for high rates of inter- and intra-oceanic gene flow in planktonic protists and widespread oceanic distributions of cryptic "sibling" species (17, 23, 27), suggest that the geographic isolation of marine diatoms cannot be maintained for long periods. Our results strongly support the hypothesis that environmental selection rather than dispersal dominates diatom community structure. To the extent that marine diatoms are a model microbial taxonomic group, our results imply that the biodiversity and macroevolutionary patterns at the microbial level fundamentally differ from those of macroscopic animals and plants, negating the idea that all living things follow similar ecological and evolutionary rules (6).

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Supporting Online Material

www.sciencemag.org/cgi/content/full/325/5947/1539/DC1

Materials and Methods

Fig. S1

Tables S1 and S2

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A Constant Flux of Diverse Thermophilic Bacteria into the Cold Arctic Seabed

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Microorganisms have been repeatedly discovered in environments that do not support their metabolic activity. Identifying and quantifying these misplaced organisms can reveal dispersal mechanisms that shape natural microbial diversity. Using endospore germination experiments, we estimated a stable supply of thermophilic bacteria into permanently cold Arctic marine sediment at a rate exceeding 10^8 spores per square meter per year. These metabolically and phylogenetically diverse *Firmicutes* show no detectable activity at cold in situ temperatures but rapidly mineralize organic matter by hydrolysis, fermentation, and sulfate reduction upon induction at 50°C. The closest relatives to these bacteria come from warm subsurface petroleum reservoir and ocean crust ecosystems, suggesting that seabed fluid flow from these environments is delivering thermophiles to the cold ocean. These transport pathways may broadly influence microbial community composition in the marine environment.

Microbial diversity surveys have revealed that species richness is determined by many low-abundance taxa—the so-called rare biosphere (1–3). In the ocean, certain

members of this relatively unexplored biosphere comprise a dormant microbial “seed bank” that can be transported passively over great distances (1). Quantitatively tracking the migration of in-

dicator taxa can highlight key factors that influence patterns of biogeography and may help evaluate the extent to which microorganisms exhibit a cosmopolitan distribution (4). Endospore germination allows certain bacteria to persist as dormant cells in hostile environments, explaining discoveries of viable thermophilic *Firmicutes* in inhospitably cold habitats (5–10). Quantitative studies of this phenomenon are scarce, and the origin and distribution of thermophiles in cold environments remain enigmatic (6–11). Thermophilic sporulating taxa such as certain *Desulfotomaculum* spp. may constitute only 0.001% of marine microbial populations (8, 12). Like the rare taxa, spores are less prone to viral lysis or predation, and are not detected by traditional diversity surveys (1, 2). A spore-forming *Desulfotomaculum* strain that can only grow between 26° and 47°C was recently isolated from permanently cold Svalbard fjord sediment in the Arctic (10). The present study assessed thermophile diversity, abundance, and distribution in Svalbard sediments to reveal insights into mechanisms governing biogeography in the marine environment.

Pristine sediment was sampled from Smeerenburgfjorden (80°N; fig. S1) and incubated over an experimental temperature range (13), which revealed two distinct sulfate-reduction regimes

(Fig. 1A). The first has a temperature optimum (T_{opt}) of 22°C and a maximum (T_{max}) of 32°C, consistent with earlier studies in Svalbard sediments (14, 15) where the in situ temperature is -2° to +4°C year-round. This temperature-activity profile is characteristic of psychrophilic sulfate-reducing bacteria (SRB) that are well adapted to cold conditions (14, 16), which explains their activity and abundance (up to 16%) in this environment (17). A second T_{opt} of 56°C (Fig. 1) indicates a previously unrecognized thermophilic community with a T_{max} above 60°C. Pasteurization at 80°C killed the psychrophiles but did not adversely affect the thermophiles (Fig. 1B), indicating that the latter exist as endospores in situ and only germinate after heating. This was supported by successful polymerase chain reaction targeting the spore-forming SRB genus *Desulfotomaculum* only if the sediment was incubated at 50°C before DNA extraction.

Psychrophilic and thermophilic communities were investigated further by incubating homogenized surface sediment at 50°C (13). Sulfate reduction rates (SRR) quickly dropped to below the detection limit (Fig. 2A) due to stimulation and subsequent death of vegetative psychrophiles as the sediment warmed up (compare to Fig. 1A). Thermophilic SRR increased exponentially between 20 and 96 hours. The transition from SRR below detection (up to 16 hours) to the onset of the exponential phase (at 20 hours) suggests a lag phase during which conditions became favorable for germination of thermophilic SRB spores. Endospore germination requires appropriate nutrients and substrates (18) such as volatile fatty acids (VFA) that are produced by microbial fermentation. VFA are typical electron donors for SRB and were generated rapidly during incubation at 50°C (Fig. 2B), creating conditions suitable for thermophilic sulfate reduction.

Several lines of evidence demonstrate that the VFA production was biologically mediated and not due to thermal alteration of the sediment organic matter. VFA did not accumulate in autoclaved sediment incubated in parallel at 50°C (concentrations never exceeded 0.3 mM). Amendment with the fluorescently labeled polysaccharides pullulan or arabinogalactan revealed extracellular enzymatic hydrolysis in sediment

incubated at 50°C, whereas no hydrolysis was detected in sediment-free controls. Clone library analyses of 16S ribosomal RNA (rRNA) genes revealed enrichment at 50°C of different bacterial groups related to *Desulfotomaculum*, *Caminicella*, and *Caloranaerobacter-Clostridiisolibacter-Thermohalobacter* lineages within the *Firmicutes* phylum (Fig. 3) [see supporting online material (SOM) and table S3]. The latter lineages are

represented by thermophilic anaerobes that convert carbohydrates and proteins to VFA, such as *Caminicella sporogenes* (19). Hydrolysis and fermentation at 50°C were therefore likely due to thermophilic spores that germinated at high temperature in the presence of complex natural organic substrates in the sediment.

VFA production at 50°C stimulated growth of a thermophilic *Desulfotomaculum* population

Fig. 1. Temperature-gradient incubations. SRR were measured in Smeerenburgfjorden sediment samples incubated between 0° and 76°C. Distinct SRB populations were active between 0° and 32°C, and between 41° and 62°C. Replicates were either untreated (A) or pasteurized for 1 hour at 80°C (B) before incubation. Open and closed symbols correspond to experiments below and above 35°C, respectively. Incubations in the thermophilic range resulted in much higher SRR (fig. S3); therefore, data are plotted as the percentage of the maximum SRR in (A) at either T_{opt} . Pasteurization killed the psychrophilic community and resulted in slightly higher activity by the thermophilic community [115% at the T_{opt} (B)].

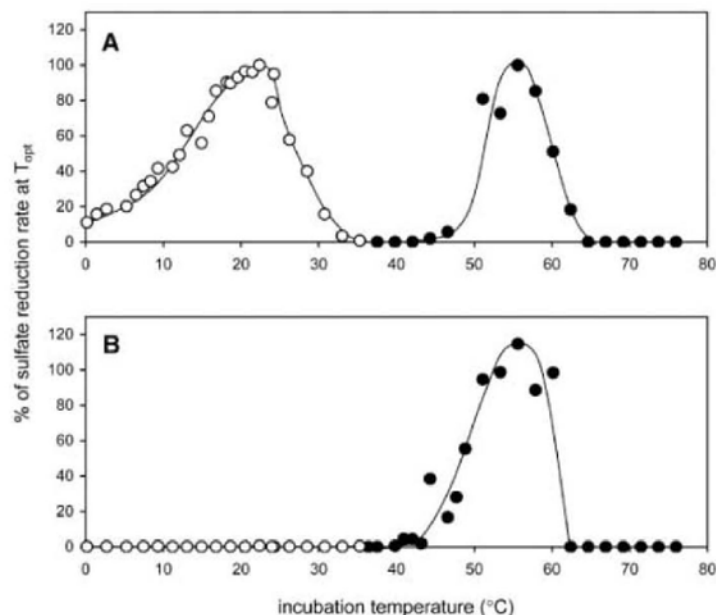
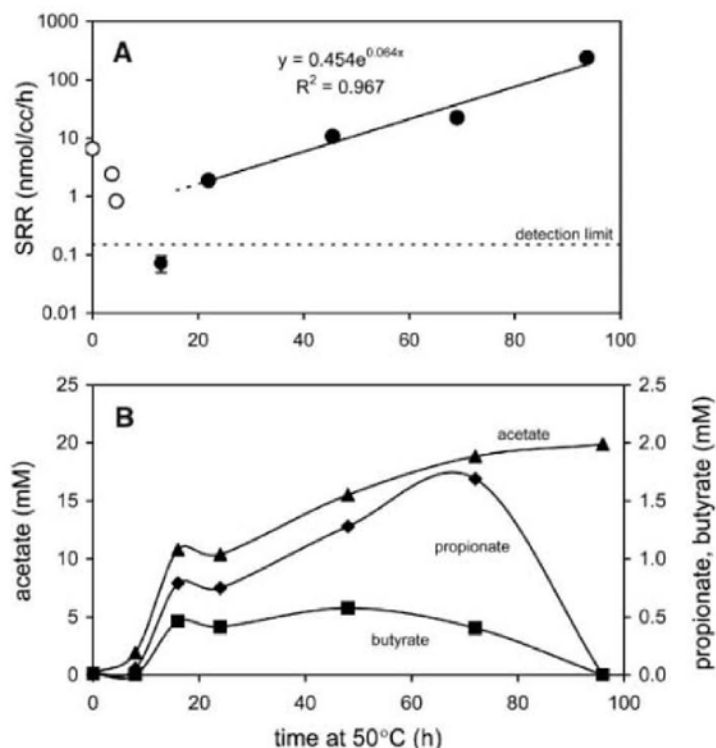


Fig. 2. Sediment incubation at 50°C. SRR (A) and concentrations of VFA (B) in Smeerenburgfjorden sediment (0- to 3-cm depth) incubated at 50°C. SRR represent 4- to 8-hour incubations with $^{35}\text{SO}_4^{2-}$ radiotracer. Open symbols correspond to the psychrophilic SRB community that was killed as the temperature increased to beyond their T_{max} (compare to Fig. 1A). SRR were below detection during the 10 to 16 hours time interval ($n = 2$; vertical bar: standard error). Sulfate reduction by 20 to 24 hours indicates germination of *Desulfotomaculum* spores, which subsequently catalyzed an exponential increase in SRR. These data constrain the earliest onset of the exponential phase to 16 hours, as indicated by the dashed extension of the exponential trendline. The exponential phase corresponded to the consumption of butyrate and propionate, which increased steeply, together with acetate (B), before the onset of thermophilic sulfate reduction.



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(Fig. 3), resulting in an exponential increase in SRR (Fig. 2A). The *Desulfotomaculum* cell density at the onset of sulfate reduction can be estimated by dividing the bulk rate ($1.3 \text{ nmol cm}^{-3} \text{ hour}^{-1}$ at 16 hours based on the exponential function in Fig. 2A) by a mean cell-specific sulfate reduction rate of $2.0 \text{ fmol cell}^{-1} \text{ hour}^{-1}$ [based on 33 pure cultures during exponential growth (20), and representative of thermophilic *Desulfotomaculum* spp.; see SOM]. This calculation estimates a population of $6.3 \times 10^5 \text{ SRB cm}^{-3}$ at 16 hours, which corresponds to the in situ spore density given that SRB growth did not occur before 16 hours (Fig. 2A).

Exponential increases in SRR were also measured across a series of intact sediment cores (0- to 23-cm depth) incubated at 50°C (13). These data indicate similar numbers of thermophilic *Desulfotomaculum* spores, on the order of 10^5 cm^{-3} , at all depths (fig. S2). Thermophiles thus constitute a stable component of the rare biosphere ($\sim 0.01\%$) in this Arctic marine habitat (17). Abundant taxa in Smeerenburgfjorden sediment are psychrophilic *Cytophaga*, *Flavobacteria*, *Gammaproteobacteria*, and *Deltaproteobacteria*

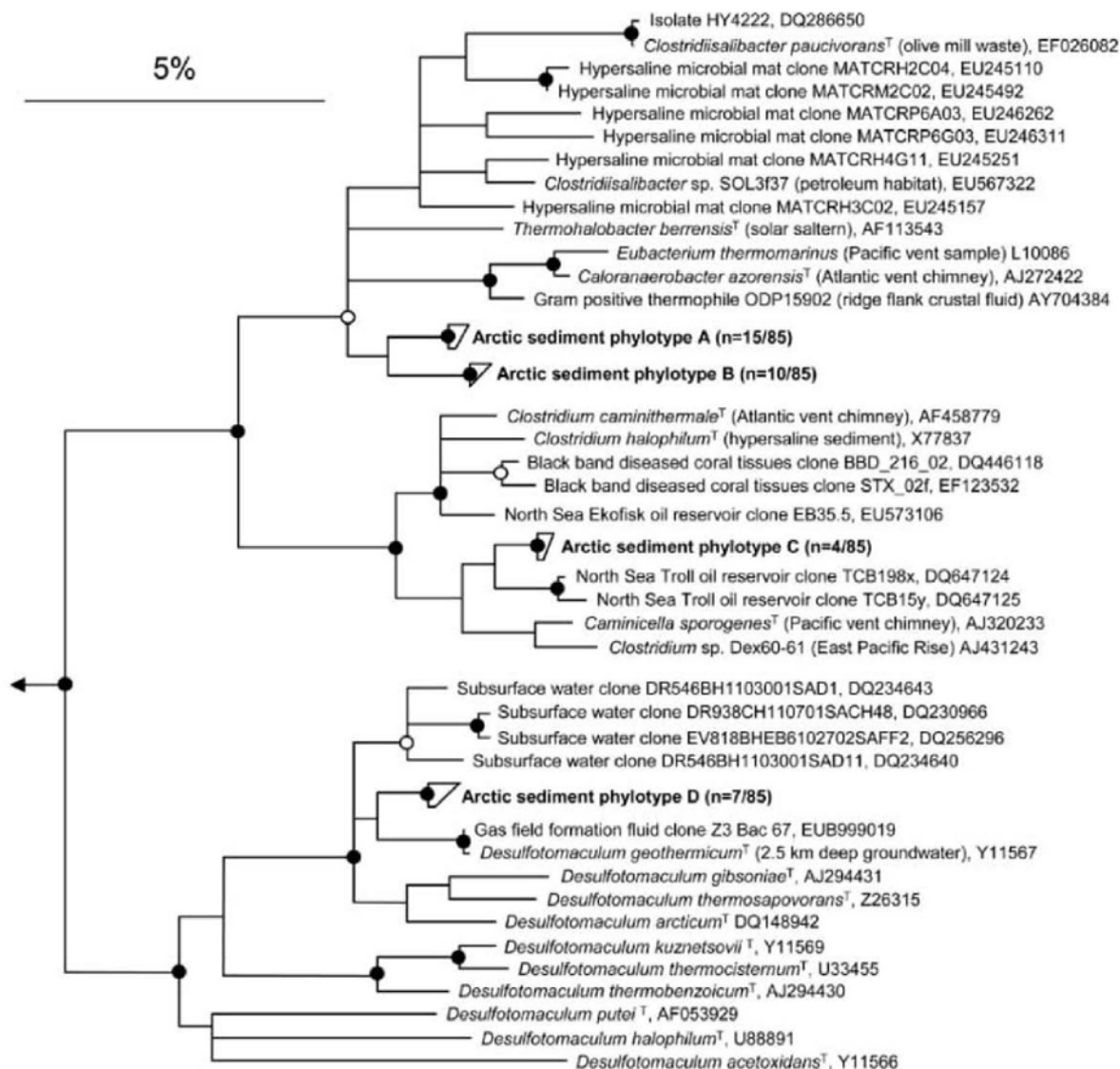
(17) that catalyze hydrolysis, fermentation, and sulfate reduction during degradation of organic matter (15, 21). We induced the same processes at 50°C , which stimulated SRR about 30-fold higher than in sediment incubated at 4°C (fig. S3). It is interesting that the thermophilic bacterial community has metabolic potential that mirrors the dominant metabolic processes occurring in situ. However, these thermophilic spores make no contribution to local biogeochemical cycling (Fig. 1). Our experience with thermophiles cultivated from Smeerenburgfjorden that have no detectable metabolic activity below 25°C supports this. Thermophilic spores must therefore be supplied externally and can be considered akin to particles accumulating in the sediment.

To estimate the particle flux of thermophilic spores into the sediment, we determined an age model by measuring the ^{210}Pb activity as a function of depth (see SOM). This revealed a sediment accumulation rate of $0.19 \text{ cm year}^{-1}$ in Smeerenburgfjorden (figs. S2 and S4). Given a stable abundance of about $10^5 \text{ spores cm}^{-3}$ with depth (fig. S2), the constant supply of thermophiles to this site is $2 \times 10^8 \text{ m}^{-2} \text{ year}^{-1}$. Other

fjords along the west coast of Svalbard have comparable thermophilic SRB densities in surface sediments (see SOM; fig. S1). The fjords and the adjacent coastal shelf in this area cover about 1000 km^2 (fig. S1), hence an extrapolation of our estimate corresponds to an annual supply of $\sim 10^{17}$ thermophiles in this Arctic region. These large numbers highlight not merely the occurrence of thermophiles in the Arctic but rather their unexpected quantity and the consistency of their flux. The warm, anaerobic environment where these bacteria originate must have sufficient geographic distribution, magnitude, and source strength to support the population sizes indicated by our data.

A limited number of marine habitats meet these criteria. Deeply buried sediments hundreds of meters below the sea floor represent warm habitats for anaerobic microbes (22). Advective flow of hydrocarbons or other fluids from these sediments can penetrate the sea floor (e.g., at mud volcanoes) and transport microscopic particles or cells up into the cold ocean (23). Sea-floor pockmarks and active cold seeps are known around west Svalbard (24) (fig. S1) and are often

Fig. 3. Phylogenetic analysis of putative spore-forming thermophilic bacteria in Svalbard sediment. Clone libraries constructed before and after incubation at 50°C differed significantly due to the enrichment of thermophilic *Firmicutes* (see SOM, tables S2 and S3). Dominant phylotypes (i.e., $>5\%$ of clones) from the 50°C sediment library are indicated in bold-face with relative abundances shown in parentheses. These phylotypes were not detected before 50°C incubation. The consensus tree of 16S rRNA gene sequences of selected *Firmicutes* includes next relatives for each phylotype (top 10) plus additional type strains (for *Desulfotomaculum*). Habitats of origin for closest relatives are indicated. Filled and open circles indicate lineages with $>90\%$ and 80 to 90% parsimony bootstrap support (100 resamplings), respectively. The scale bar indicates 5% sequence divergence as estimated from maximum-likelihood analysis.



associated with deep gas or oil-bearing deposits (23). 16S rRNA gene sequence comparisons revealed that taxa enriched in our 50°C experiments (Fig. 3) are most closely related to bacteria from subsurface petroleum reservoirs or oil production facilities (94 to 96% similarity; table S3). Another source of thermophiles could be nearby mid-ocean ridge spreading centers (fig. S1). Large volumes of fluids circulating through ocean crust (25) could transport cells away from warm anoxic niches in this seafloor habitat (26) and suspend them in abyssal currents. The closest relatives to the Arctic thermophiles also include an anaerobic thermophile isolated from deep, hot crustal fluid (94% similarity; table S3) (27).

Petroleum-bearing sediments and fractured ocean crust both host anaerobic heterotrophic microbial communities (26, 28). Areas of discharge connecting these habitats to the water column are widespread, and both processes expel large volumes of fluid into the oceans (23, 25). A combination of different point sources could explain the diversity and distribution of thermophilic taxa in Arctic sediments (Fig. 3 and fig. S1). Although our observations suggest that seabed fluid flow governs the biogeography of thermophilic spore formers, these passive dispersal mechanisms are unlikely to act only on these particular bacteria. Permeable conduits through sediments and ocean crust pass through several microbial niches with changing local temperature

and geochemistry (22, 25, 26). Widespread seeding of the oceans by geofluids from deep biosphere habitats may therefore contribute broadly to the high microbial diversity observed in the marine environment.

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Supporting Online Material

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Materials and Methods

SOM Text

Figs. S1 to S4

Tables S1 to S3

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Three-Dimensional Structural View of the Central Metabolic Network of *Thermotoga maritima*

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Metabolic pathways have traditionally been described in terms of biochemical reactions and metabolites. With the use of structural genomics and systems biology, we generated a three-dimensional reconstruction of the central metabolic network of the bacterium *Thermotoga maritima*. The network encompassed 478 proteins, of which 120 were determined by experiment and 358 were modeled. Structural analysis revealed that proteins forming the network are dominated by a small number (only 182) of basic shapes (folds) performing diverse but mostly related functions. Most of these folds are already present in the essential core (~30%) of the network, and its expansion by nonessential proteins is achieved with relatively few additional folds. Thus, integration of structural data with networks analysis generates insight into the function, mechanism, and evolution of biological networks.

The advent of genome sequencing has enabled development of computational and experimental tools to investigate complete biological systems, but it has also highlighted the difficulty in integrating complex information for the hundreds to thousands of different molecules that compose even the smallest biological networks. Such integration presents many challenges, especially when assembling data from

diverse fields, such as biochemistry and structural biology, that use different operational languages and conceptual frameworks. Biochemistry has traditionally focused on individual reactions and pathways, but recent advances in genomics have led to more rapid growth in the reconstruction and modeling of metabolic networks on a genome-wide scale (1–3). Thus, biochemical reactions, pathways, and networks can now be described in

the context of entire cells, thereby enabling more realistic simulations of the behavior of metabolic networks in a growing number of organisms (4–7). Nevertheless, metabolism is still generally defined in terms of the chemical names and identity of substrates, products, and reactions. It does not explicitly consider the three-dimensional structures of its components, although such knowledge is required for a comprehensive understanding, not only of the individual reactions, but more importantly, of metabolic networks as a whole. Without such knowledge, we cannot rigorously define enzyme mechanisms or

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predict the effects of mutations or drugs; on the global level, we cannot understand the evolutionary relationships between different pathways, how new metabolic capabilities are acquired, and how individual organisms adapt to their particular ecological niches and respond to environmental pressures.

Such an understanding can be provided by structural biology, which has traditionally focused on individual proteins outside of their full, system-level, biological context. The emergence of large-scale structure genomics projects, such as the Protein Structure Initiative (8), has provided an exciting new opportunity for structural biology to contribute on a scale similar to that of genomics.

Thermotoga maritima, one of the first discovered hyper-thermophilic bacteria (9), represents the deepest known lineage of eubacteria (9, 10), has one of the smallest genomes for a free-living organism (11), and has been the sub-

ject of extensive experimental analysis (12, 13), making it an ideal model organism for systems biology and for integration of biochemical and structural approaches (14).

We constructed a metabolic model of *T. maritima* by a bottom-up approach, which first identified all known biochemical reactions and substrates from almost 150 publications (table S3), providing direct biochemical, genomic, and physiological evidence for more than 50% of the metabolic reactions. We then identified the remaining reactions from high confidence, homology-based annotation databases (15, 16) and from experimental or modeled protein structures (see below). We used flux balance analysis (17) to test the completeness of the network, revealing gaps, such as missing enzymes or redundant functional assignments, which were then resolved by manual curation for individual cases. We continued iterative evaluation of the network until its performance reproduced, in silico, the ex-

perimentally determined metabolic capabilities of *T. maritima* (tables S9 and S10) (18).

Our resulting metabolic reconstruction included 478 metabolic genes, 503 unique metabolites, and 562 intracellular and 83 extracellular metabolic reactions (18), and it reproduced *T. maritima*'s ability to grow on diverse carbohydrates (table S9) and to produce known metabolic by-products; e.g., acetate and hydrogen. The overall scope, content, and quality of this metabolic reconstruction were comparable with state-of-the-art reconstructions for other model organisms (table S6). Although the current model does not yet provide an exhaustive description of *T. maritima* metabolism, it represents a major step in an iterative process of annotation and modeling of this organism.

The *T. maritima* metabolic reconstruction (mr) defines a specific set of proteins (mrTM) that carry out the biochemical functions that make up a self-sustaining, metabolic network. Of

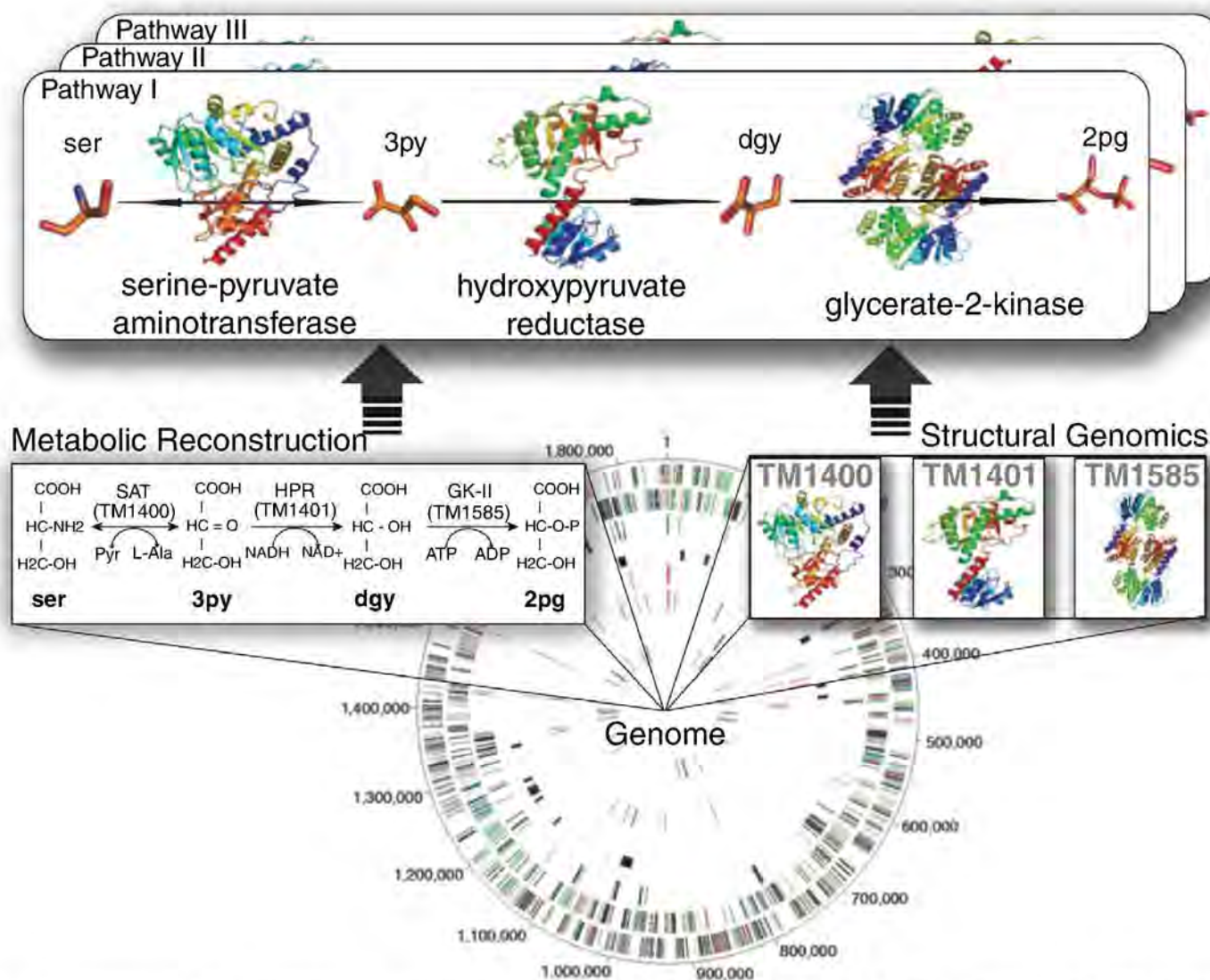


Fig. 1. Combining metabolic reconstruction and structural genomics approaches for an integrated annotation of the *T. maritima* central metabolic network. Underlying genomics information (Bottom) enabled both a metabolic reconstruction (Left) and an atomic-level structure

determination/modeling of *T. maritima* proteins (Right). Integration of these two approaches enabled detailed information to be acquired for every reaction in the network (Top); an example from the *T. maritima* serine degradation pathway is illustrated (32).

478 proteins in this mrTM set, structures of 120 proteins have been determined experimentally (12), and 358 were predicted and modeled with a variety of computational approaches (18). The quality of the modeled structures spans the spectrum from those comparable to low-resolution, experimental structures (190 were built on templates with more than 30% identity to the targets) to very approximate (52 were based only on fold predictions). For three (TM1444, TM0788, and TM0540), the automated structure prediction approach failed, and approximate structures were modeled by combining several different fold prediction algorithms with manual refinement (18). Quality control, as based on public benchmarks in modeling and fold recognition, suggests

high confidence that all models are correct at the fold-assignment level (18). Thus, these combined approaches allowed us to achieve complete structural coverage for the mrTM set (Fig. 1).

The information from structural determination of *T. maritima* proteins and their homologs provided additional support for functional assignment of 181 individual genes. A total of 41 experimental structures of *T. maritima* proteins contained relevant metabolites, and 140 crystal structures (used as templates for homology modeling) were also determined as complexes with ligands, all of which support the functional assignment in the reconstruction. In at least two cases, TM0449 (19–22) and TM1643 (23), structural analysis was critical for identification of

enzymatic function and, in many other cases, substantially contributed to assignment of function.

Metabolic reconstruction not only can be described in a matrix format that can directly be used for metabolic simulations to predict essential genes or growth rates, it can also be represented as a graph. Because the reconstruction represents a fully functional, cell-level model of a metabolic network, analysis of the topology of this graph allows us to answer many interesting questions, especially when combined with knowledge of structures or models for all proteins in the network. For instance, what is the dominant mechanism for expansion of a metabolic network in a single organism? In the “patchwork” hypothesis (24), network expansion is driven by recruitment

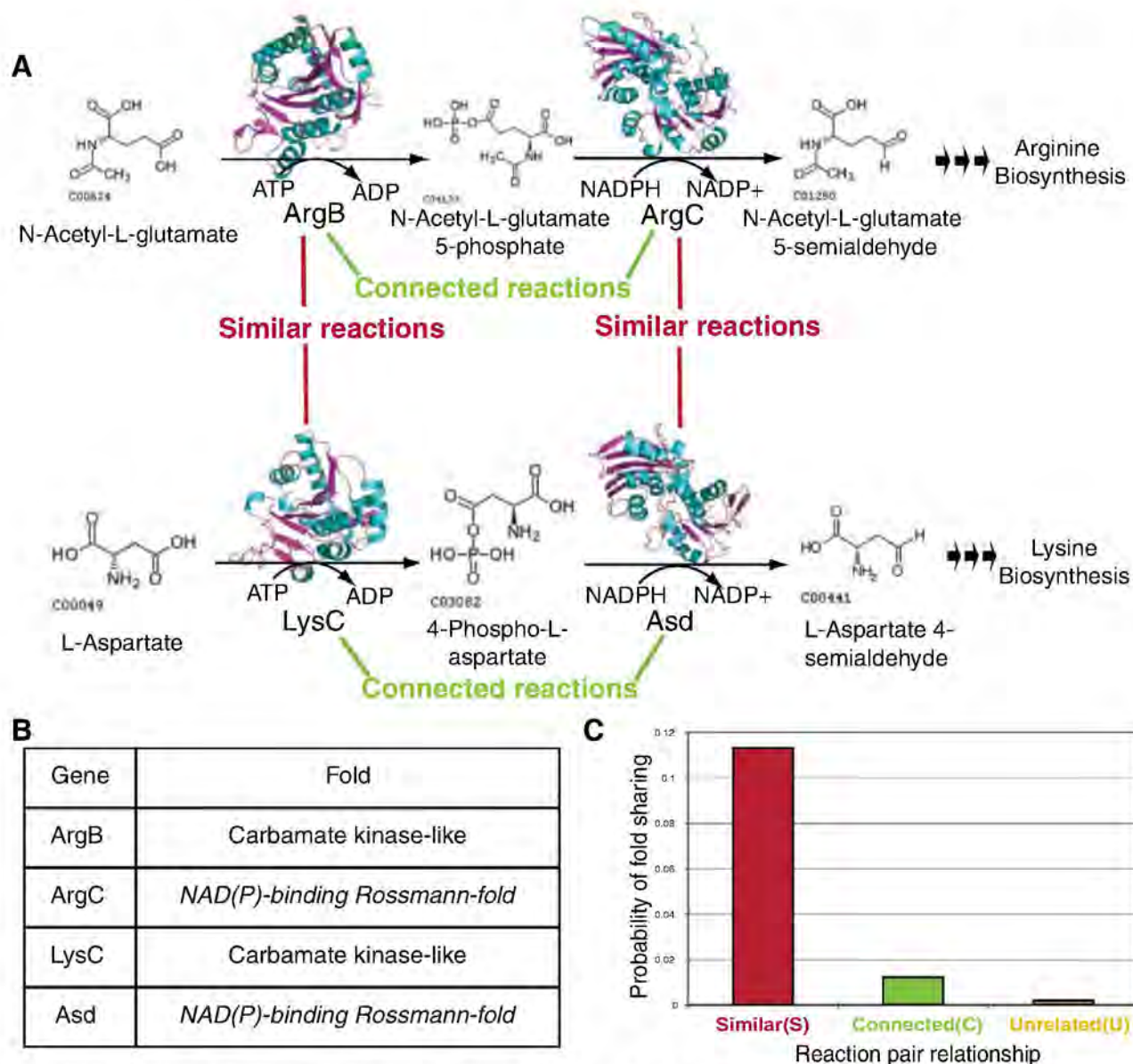


Fig. 2. Classification of metabolic reactions. **(A)** Examples of similar (S), connected (C), and unrelated (U) reactions from the arginine and lysine biosynthesis pathways. ArgB and LysC share a co-substrate [adenosine triphosphate (ATP)] that undergoes the same transformation [to adenosine diphosphate (ADP) + Pi]. Similarly, ArgC and Asd transform the reduced form of NADP⁺ (NADPH) to nicotinamide adenine dinucleotide phosphate (NADP⁺). By these criteria, both pairs are classified as similar. At the same time, reaction

pairs ArgB/ArgC and LysC/Asd are adjacent in the pathway, because the product of the first reaction is the substrate for the next. These reaction pairs are classified as connected. All other pairs of reactions (ArgB/Asd and ArgC/LysC) are classified as unrelated. In this example, only the enzymes classified as similar (ArgB/LysC and ArgC/Asd) have the same fold. **(B)** Detailed information on the enzymes in (A). **(C)** Bars representing the relative number of pairs with the same fold in each category of reactions.

of proteins that perform similar reactions but are present in distinct pathways. Conversely, in the “retrograde” hypothesis (25), proteins evolve, after duplication, to perform dissimilar reactions within the same pathway or neighboring part of the network. Analysis of fold conservation as a function of network topology, therefore, addresses this key issue. Similar analyses have been performed previously on a small set of known pathways (26, 27), but our integrated approach allowed us to analyze the complete set of pathways that form the fully functional, self-sustained metabolic network of a single organism.

We then established an automated protocol to classify metabolic reactions into three categories: (i) similar, (ii) connected, and (iii) unrelated (Fig. 2 and fig. S6). Enzymes that catalyze similar types of reactions have a sixfold higher probability of having the same fold than enzymes catalyzing connected reactions (Fig. 2C), supporting the patchwork hypothesis (24). However, it should be noted that proteins catalyzing connected reactions still have a higher chance of having the same fold as those catalyzing unrelated reactions, suggesting a role for gene duplication within pathways during pathway evolution (i.e., the retrograde model). More importantly, the patchwork hypothesis can account for only 11% of the observed structural similarity between mrTM proteins of similar function, indicating that convergent evolution of similar reaction mecha-

nisms [i.e., nonhomologous gene displacement (28), where two nonhomologous proteins perform the same or similar metabolic function] is not a rare event and substantially contributes to evolution of the central metabolic network.

Another interesting question is the distribution and frequency of protein folds in this mrTM set. The 478 proteins contain 714 domains, but only 182 distinct folds, which are significantly fewer than would be expected (~300) for an equivalent random set of proteins with known structures (fig. S8). The surprisingly small number of folds arises from the fact that the most popular folds [e.g., the P-loop, triosephosphate isomerase (TIM) barrel, and Rossmann folds] are overrepresented as compared with their frequency in the general protein population (Fig. 3). Some relatively rare folds, abundant in the mrTM set, such as the biotin synthetase and the thiamin diphosphate binding folds, include groups of enzymes that perform specific but essential functions, such as tRNA aminoacylation or carbon metabolism.

The most obvious interpretation of this skewed fold distribution is that the mrTM set, which covers the most fundamental protein functions, consists of the most ancient and, thus, the most abundant protein families. To probe this interpretation further, we analyzed the fold distribution for the core of the *T. maritima* metabolic network, as represented by the set of essential proteins. We identified essential proteins by a

reductive evolution simulation approach (18, 29), where iterative simulations are performed to identify a minimal network by randomly eliminating genes from the model until additional elimination would result in a nonviable network. Each simulation led to a different minimal network, of size anywhere between 200 and 300 genes (i.e., corresponding to 42 to 63% of the mrTM set). Statistical analysis of 1000 such minimal networks in independent simulations in glucose minimal medium (18) allowed the classification of genes from the mrTM set into three categories: (I) core- or unconditional-essential genes that are always present, (II) nonessential genes that never appear, and (III) “synthetic lethal” or “conditional-essential” genes (30) that appear only in some simulations, but not in others, depending on which other genes are removed or retained in a particular network minimization. For example, if two genes have the same essential function, the deletion of either gene would not be lethal, but at least one gene has to be present in the minimal network. The frequency of such genes in multiple simulations reflects the topology of the network and the relative redundancy of gene functions in the network. It is important to emphasize that the core-essential genes would not be sufficient to maintain a viable metabolic network, as all of the many possible minimal networks contain constant (core-essential genes) and variable (subset

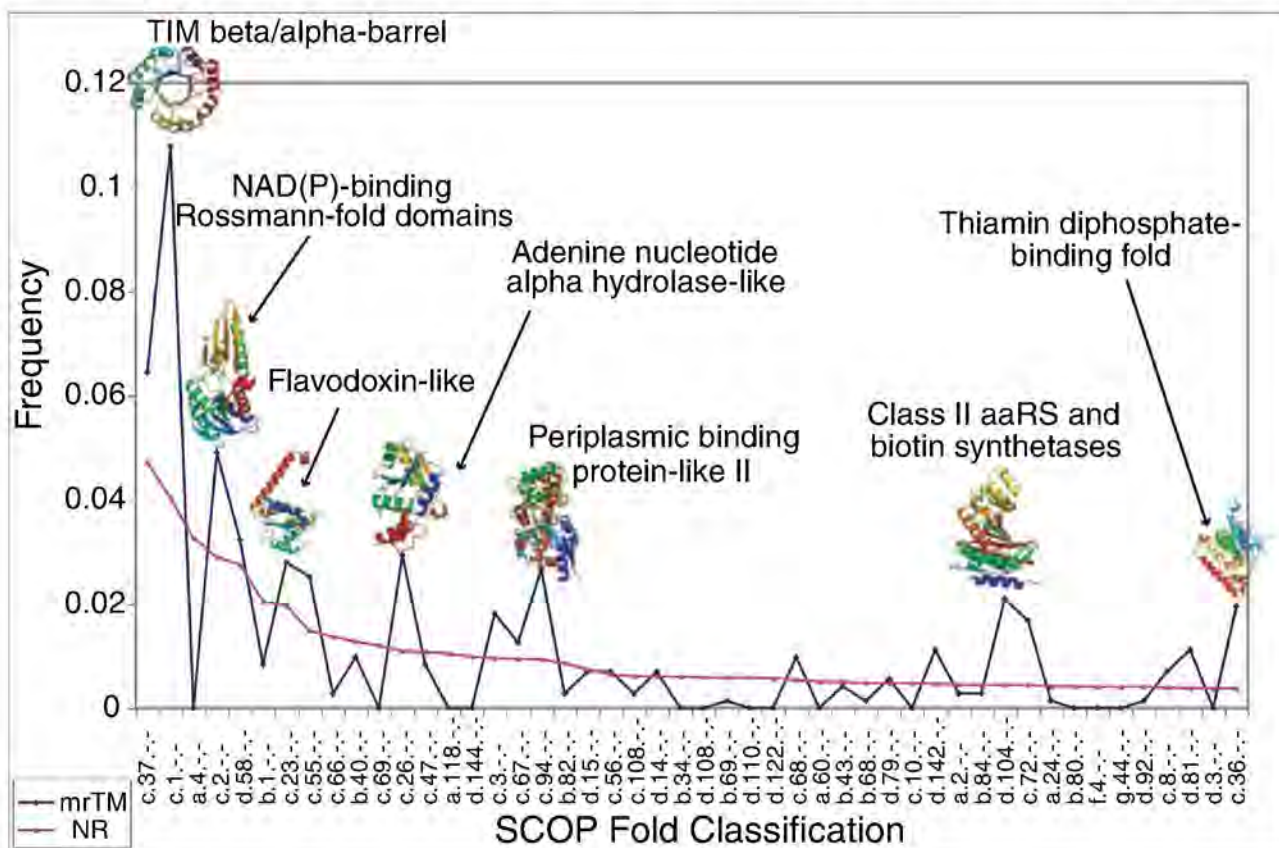


Fig. 3. Distribution of folds in the mrTM protein set with the most over-represented folds, illustrated by structural ribbon diagrams. Fold codes from the Structural Classification of Proteins (SCOP) database (33) are shown on the

x axis with the observed frequency on the y axis. The expected frequency for each fold in the NCBI nonredundant database (31) is shown as a magenta trace. TIM, triosephosphate isomerase.

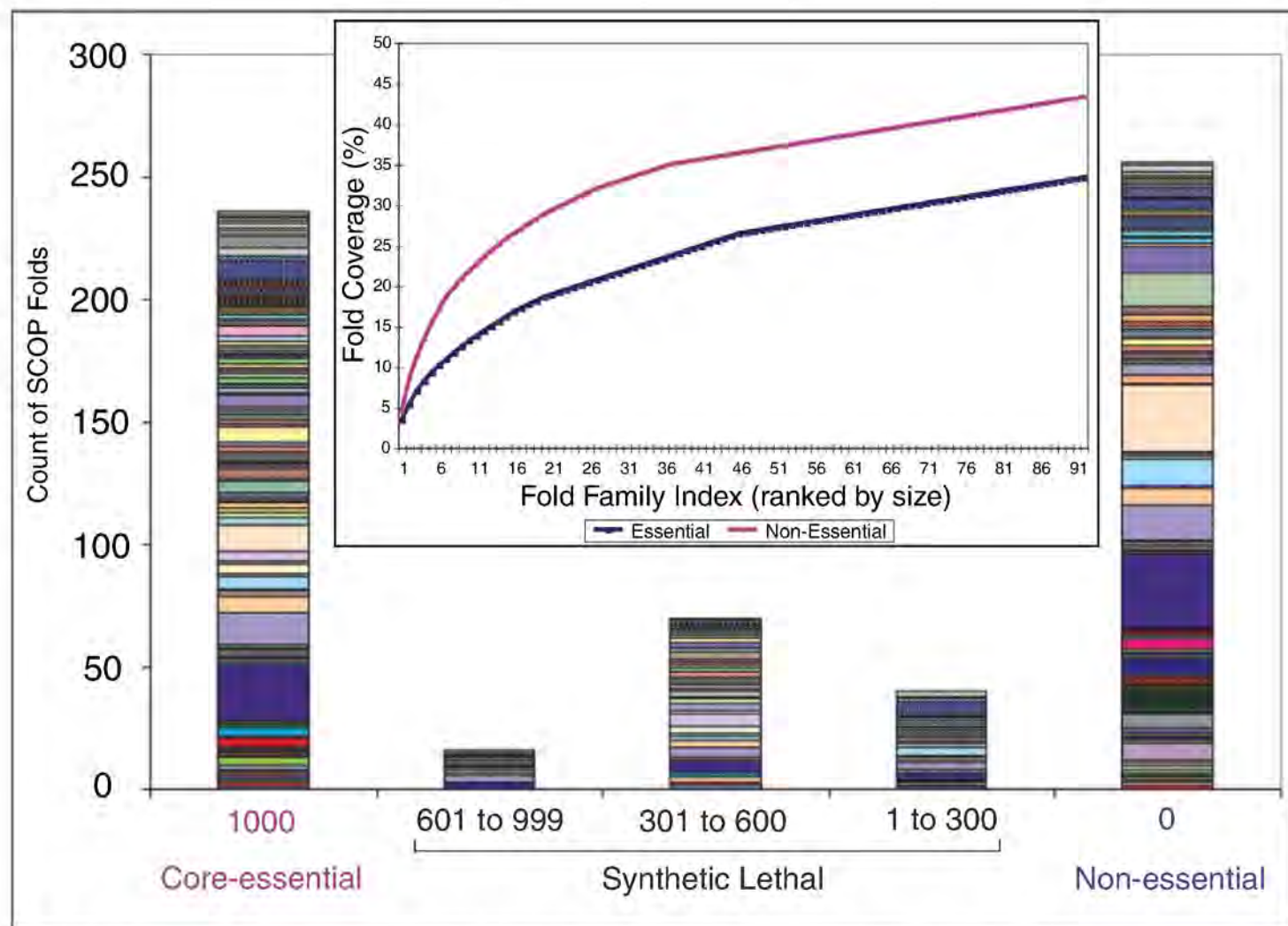


Fig. 4. Fold composition of the nonessential, synthetic lethal, and core-essential protein sets (see text for details) illustrated by colors associated with different folds (see fig. S9 for details). The x axis represents the number of simulations that resulted in identification of core-essential (1000 appearances in 1000 simulations), synthetic lethal (from 999 to 1), and nonessential genes (0);

and the y axis indicates their classification into SCOP fold categories. (**Inset**) Cumulative fold coverage of core-essential and nonessential protein sets (blue, core-essential; magenta, nonessential). The fold distribution in all three groups is different, although core-essential and nonessential sets have some weak similarity, more than either group compared with synthetic lethal sets.

of conditionally essential genes) components. The mrTM set consists of 177 core-essential, 203 nonessential, and 98 conditional-essential genes. Proteins in these three sets have very different fold distributions (Fig. 4). The number of folds in the core-essential group is surprisingly large for its sample size (111 folds for 177 proteins) as compared with the nonessential group, which contains more proteins but a smaller number of folds (92 folds for 203 proteins). This trend is inverse to that observed when mrTM is compared with nonredundant sequences in the National Center for Biotechnology Information (NCBI) database (31) (fig. S8), where the mrTM set was more abundant in popular folds. These analyses suggest that core-essential proteins perform unique chemical functions that are strongly associated with specific folds and are so fundamental that their deletion would result in a nonviable network.

We have presented here the integration of a metabolic and structural view of the central

metabolic network of the thermophilic bacterium *T. maritima*. Achieving a complete description on these two levels is an important milestone that now enables large-scale analyses, such as the network-scale comparison of correlations between fold conservation and biochemical function. From our study, not only can we provide a quantitative estimate of the dominance of the patchwork model (24) versus the retrograde model (25) of metabolic evolution, but we can also illustrate the importance of convergent or parallel evolution in proteins carrying out similar biochemical functions. Furthermore, we show that the set of proteins responsible for the central metabolism in *T. maritima* is highly nonrandom and dominated by a small number of folds that significantly exceed their already dominant distribution in the protein universe, suggesting that the central metabolism network has evolved mainly from a set of the most ancient proteins that have had sufficient time to develop divergent functionalities and, hence, expand into the very

large and very diverse protein families that we observe today. At the same time, the subset of core-essential proteins reverses this trend and is relatively more diverse than an equivalent subset of nonessential proteins. This counterintuitive situation is attributable to the presence of some specific folds with functions that are so unique that it is impossible to replace them with other existing folds.

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34. We specifically acknowledge the invaluable work of individual crystallographers at the JCSG and other Protein Structure Initiative (PSI) centers, as well as individual research groups, who have solved structures analyzed here, either directly or that we used as modeling templates. The full list of these proteins is provided in the supporting online material. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of General Medical Sciences (NIGMS). This work was supported by the NIH PSI grants P20 GM076221 (JCCM) and U54 GM074898 (JCSG) from the NIGMS; grant DE-FG02-08ER64686 from the Office of Science (Biological and Environmental Research), U.S. Department of Energy; and the Gordon and Betty Moore Foundation CAMERA project.

Supporting Online Material

www.sciencemag.org/cgi/content/full/325/5947/1544/DC1

Materials and Methods

Figs. S1 to S9

Tables S1 to S13

References

Metabolic reconstruction in SMBL and MATLAB formats

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Details of Insect Wing Design and Deformation Enhance Aerodynamic Function and Flight Efficiency

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Insect wings are complex structures that deform dramatically in flight. We analyzed the aerodynamic consequences of wing deformation in locusts using a three-dimensional computational fluid dynamics simulation based on detailed wing kinematics. We validated the simulation against smoke visualizations and digital particle image velocimetry on real locusts. We then used the validated model to explore the effects of wing topography and deformation, first by removing camber while keeping the same time-varying twist distribution, and second by removing camber and spanwise twist. The full-fidelity model achieved greater power economy than the uncambered model, which performed better than the untwisted model, showing that the details of insect wing topography and deformation are important aerodynamically. Such details are likely to be important in engineering applications of flapping flight.

Insects achieve remarkable flight performance with a diverse range of complex wing designs (1, 2). Computational fluid dynamics (CFD) offers an opportunity to identify the features underpinning the aerodynamic performance of insect wings. By comparing numerical simulations of different designs, it is possible to test the effects of modifications that may be outside the natural range of variation. Unfortunately, a lack of detailed measurements of insect wing kinematics has limited previous numerical studies of insect flight to two-dimensional (2D) models (3–6) or to 3D models in which the wings are modeled as rigid flat plates (7–11) or as rigid sections with constant camber and twist (12). Such simplifications can dramatically change the conclusions drawn about flow struc-

ture (13), and no model has yet been validated experimentally against flow visualizations from a real insect. We used the most detailed set of insect wing kinematics published to date (2) to develop the first 3D CFD model of an insect with deforming wings. We validated the results of our CFD simulations against qualitative and quantitative flow visualizations of real locusts. We then used progressive simplifications of the wing kinematics to analyze the aerodynamic consequences of the measured twist and camber.

We modeled a typical wingbeat of the desert locust *Schistocerca gregaria* (14) by averaging the kinematics of four consecutive wingbeats from one of the individuals described in (2). These kinematics were obtained by using four high-speed digital video cameras to track more than 100 natural features and marked points on the wings, which were then used to reconstruct the deforming surface topography of the wings with a mean spatial error of 0.11 mm (15). We fitted cubic splines to the wing outline and veins, and we interpolated these spatially to give the surface mesh for the CFD simulations, which we

then interpolated temporally to give up to 800 time steps per wingbeat (14). We gave the modeled wings a nominal constant thickness of 0.05 mm based on published cross-sections of the wing veins and membrane (16). We did not attempt to model variations in thickness due to wing venation. Folding of the hindwing against the thorax could not be modeled exactly, and we instead modeled the hindwing as if it were joined to the thorax along its chord (14).

We solved the unsteady incompressible Navier-Stokes equations assuming laminar flow using a commercial CFD package (14). We constructed the CFD grid for the locust kinematics in multiple parts by using commercial software, and we incorporated the wing motions via a look-up table prescribing the kinematics (14). The wings and body were meshed with a triangular surface grid and surrounded with a thin boundary-layer grid to provide adequate resolution of velocity gradients normal to the surface. These were then surrounded with stationary outer regions representing the wind tunnel, and a deforming inner region in which the wings and boundary layer grids moved. A symmetry plane running through the sagittal plane of the insect was used. Aerodynamic forces on the wings and body were calculated by integrating pressure and viscous shear stress over the surfaces. Starting transients in the calculated aerodynamic forces vanished rapidly within the first wingbeat, with very close agreement between wingbeats thereafter, so we allowed the simulation to run for four repeated wingbeats. Aerodynamic power requirements were calculated by integrating the inner product of the local pressure and viscous forces with the local wing surface velocity in a coordinate system fixed to the insect's body.

We validated our CFD method against an independent CFD algorithm (17) by using our method to replicate published force computations for a simple model of a flapping dragonfly wing in hover (11, 14). The predicted instantaneous vertical force coefficients from the two algorithms were in excellent agreement, with a linear

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correlation coefficient of 0.99 over the course of the wingbeat. To verify the grid-independence of the CFD simulations, we performed computations with several levels of grid and time-step refinement of the locust kinematics data (14). The baseline grid consisted of 1.12×10^6 volume cells and used 200 time steps per wingbeat. We compared our baseline results with a refined grid consisting of 4.11×10^6 volume cells (14) and with the baseline grid using 400 or 800 time steps per wingbeat. We found no significant variation in force and power results as the grid was refined or the number of time steps was increased, and we therefore used the baseline grid with 200 time steps per wingbeat for the remainder of our simulations.

We also validated the results of the CFD simulation against flow visualization data from real locusts by comparing the predicted flow structures with qualitative smoke visualizations and quantitative digital particle image velocimetry (DPIV) measurements at the same position mid-wing (14, 18). The CFD simulation captures the overall structure of the flow field with remarkably high fidelity throughout the wingbeat (Fig. 1). The CFD also shows a reasonably close quantitative fit to the DPIV data, although because each of the three different techniques was applied to a different individual, we do not expect to see an exact match. The main difference between the results of the three techniques is in the presence of smaller-scale flow features in the DPIV and smoke visualizations. In particular, the roll-up of the shear layer trailing the wing is not particularly well matched by the CFD: The shear layer is present in the simulation, but the grid is apparently not fine enough to capture the detail of wake instabilities behind the trailing edge. Further DPIV flow visualizations showing the consistency of the measured flowfield between different wingbeats are shown in fig. S4.

DPIV also offers the opportunity for a detailed quantitative validation of the computed flow field. We compared a published downwash distribution measured using DPIV (18) with the results of our CFD model at the same stage mid-downstroke (Fig. 2). The CFD model closely captures the shape and magnitude of the measured downwash distribution at the position shown, which is approximately one chord length behind the hindwings. Once again, we do not expect an exact match, because the DPIV measurements (18) were made on an individual different from the one on which the kinematics measurements that we used for the CFD simulation were made (2).

To investigate the effect of detailed wing shape and kinematics, we reran the CFD simulation with two progressively simplified sets of wing kinematics (Fig. 3). In the first simplified model, termed “uncambered,” we removed the corrugation and camber of the wings while retaining the same local instantaneous twist and angle of attack along the wing. We did this by replacing the cambered chord with a straight line

connecting the leading and trailing edge (rear wing) or a straight line at the same mean incidence (forewing). In this simplified model, the wings undergo the same torsional deformation along the span as the real wing does.

In the second simplified model, termed “untwisted,” we also removed torsional deformation along the span, by replacing the forewing with a flat plate of the same instantaneous projected area and same instantaneous angle of attack at the mid-wing position. The hindwing

was replaced with two flat plates of the same total instantaneous projected area, joined along a line running from the axilla to a point midway between the fourth and fifth anal veins at the trailing edge. This allowed us to match the mid-wing angle of attack while avoiding unrealistic motions at the wing root. In this simplified model, the wings undergo the same wholesale rotation about their base as the real wing does, but the modeled wings undergo no torsional deformation.

Fig. 1. Validation of CFD simulation using full-fidelity wing kinematics (left column: 3.3 m/s free stream, 9° body angle), against DPIV measurements (middle column: 3.5 m/s free stream, 7° body angle) and smoke visualizations (right column: 3.3 m/s free stream, 9° body angle). Data are shown at four consecutive stages (A to D) of the wingbeat, beginning with the start of the downstroke, for the vertical plane that intercepts the hindwing at the mid-wing position when the wing is horizontal. The CFD and DPIV figures plot flow velocity vectors in a body-fixed reference frame and are colored according to the vertical downwash speed. For clarity, only every fifth vector is plotted in the DPIV figures. Further replicates of the DPIV data are available in fig. S4. Overall, the numerical simulation captures the empirical structure of the flow field with remarkably high fidelity. Figure S5 shows the equivalent CFD simulations for the two simplified wing kinematics models, which do not capture the empirical structure of the flow field with such fidelity.

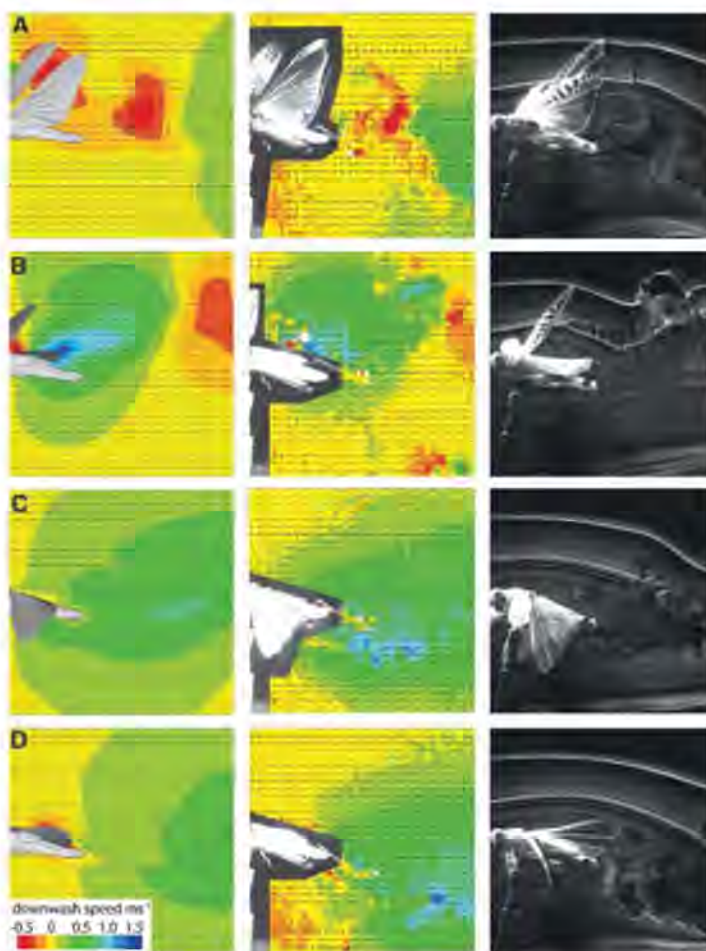
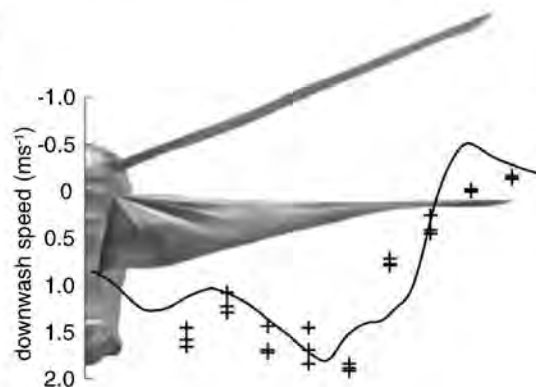


Fig. 2. Computed downwash distribution (solid line) from the CFD simulation using full-fidelity wing kinematics, validated against published DPIV measurements (crosses) of the downwash (18). The measurements are made approximately one mean chord length behind the trailing edge of the hindwing. The data represent the stage mid-downstroke shown in Fig. 1B, and the three different data points at each spanwise station represent measurements made on different wingbeats from one individual. The simulation accurately captures the measured turning points in the downwash distribution at about one-third and two-thirds of wing length and also the crossing to upwash near the wingtip.



Both simplified kinematics models preserve the gross changes in projected and wetted wing area that result from corrugation and folding of the hindwing (2). The wetted area of the hindwing in the full-fidelity model varies by as much as 14%, which reflects folding of the wing against the thorax. The wetted area of the hindwing in the untwisted model varies by as much as 19%, and the 5% difference here reflects the fact that the untwisted wing does not corrugate, because it is modeled as a flat plate.

The computed surface pressure field for the full-fidelity model shows no evidence of leading-edge separation, with the locally varying camber ensuring that the leading edge is well aligned with the oncoming flow at all times (Fig. 3A). In contrast, the untwisted kinematic model shows massive separation on the hindwing mid-downstroke, when the downward velocity of the wing is maximal, as evidenced by a low-pressure region extending over much of the wing's upper surface at this time (Fig. 3C). The uncambered model also shows evidence of separation, but with the low-pressure region confined to the basal part of the hindwing (Fig. 3B). The 2D flow fields plotted in the bottom row of Fig. 3 confirm

that flow separation is present in the two simplified models. Flow reversal is clearly visible over the hindwing for both the uncambered (Fig. 3B) and untwisted (Fig. 3C) models, but there is no evidence of flow reversal with the full-fidelity kinematics (Fig. 3A). This difference is present despite the hindwing angle of attack being identical among simulations in the 2D plane shown in Fig. 3, and it must therefore result from a combination of 3D effects and camber.

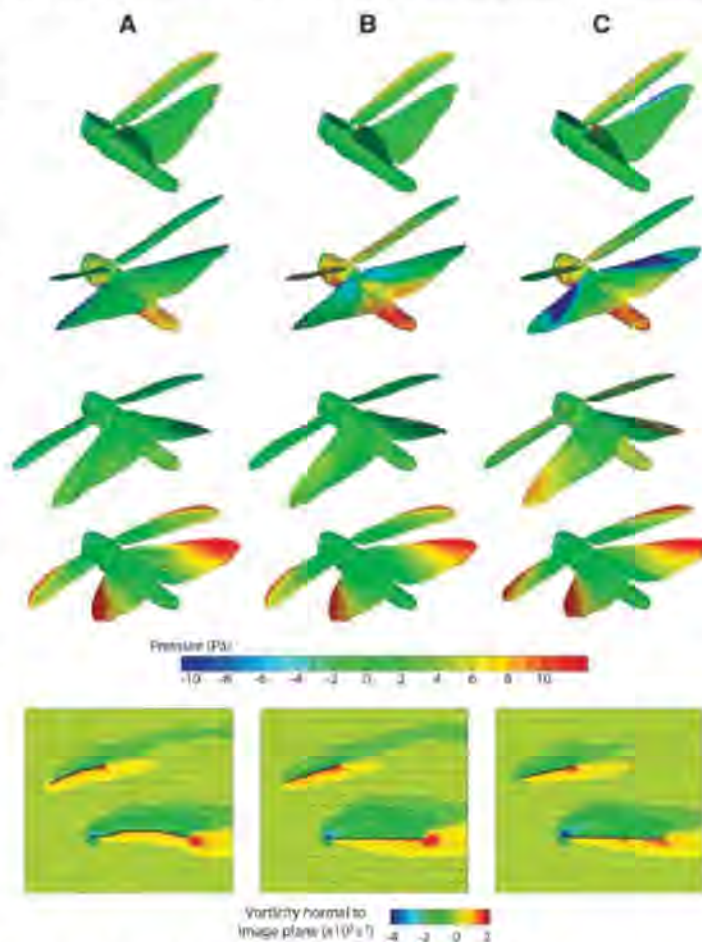
We compared the computed aerodynamic forces and aerodynamic power requirement for the full-fidelity, uncambered, and untwisted kinematics models (Fig. 4). The aerodynamic force is resolved into a lift component normal to the free stream and a thrust component parallel to it. The uncambered wings generate less lift and thrust during the downstroke than the full-fidelity wings do, because of the absence of the positive camber present on the real wings. The uncambered wings generate a similar amount of lift to the full-fidelity wings through most of the upstroke, however, which is presumably because the real wings flatten and feather on the upstroke and are therefore better approximated by the uncambered model. The same features are reflected

in the aerodynamic power requirement, with the uncambered wings requiring slightly less power than the full-fidelity wings on the downstroke but needing similar aerodynamic power on the upstroke. The pattern is more complicated for the untwisted wings, which nevertheless produce less lift and thrust than the full-fidelity model does and require greater aerodynamic power to do so.

The aerodynamic advantages of the full-fidelity wing kinematics are clearly revealed by comparing the total power economy of the different models, defined as the ratio of time-averaged total force to time-averaged total power. The total power economies in the uncambered (0.98 N W^{-1}) and untwisted (0.84 N W^{-1}) models are 7% and 15% lower, respectively, than the total power economy of the full-fidelity model (1.06 N W^{-1}). This lower efficiency of momentum transfer is attributable partly to the leading-edge separation that occurs on the hindwings in the simplified models. In addition, the simplified wing kinematics cause the resultant force to have a less favorable direction, as can be seen from the large decrements in lift and thrust in Fig. 4. This results in an even greater reduction in lift power economy, defined as the ratio of time-averaged lift to time-averaged total power: The lift power economy of the uncambered wings (0.78 N W^{-1}) is 12% lower than that of the full-fidelity model (0.88 N W^{-1}), whereas the lift power economy of the untwisted wings (0.51 N W^{-1}) is 35% lower. In summary, wing deformation in locusts is important both in enhancing the efficiency of momentum transfer to the wake and in directing the aerodynamic force vector appropriately for flight.

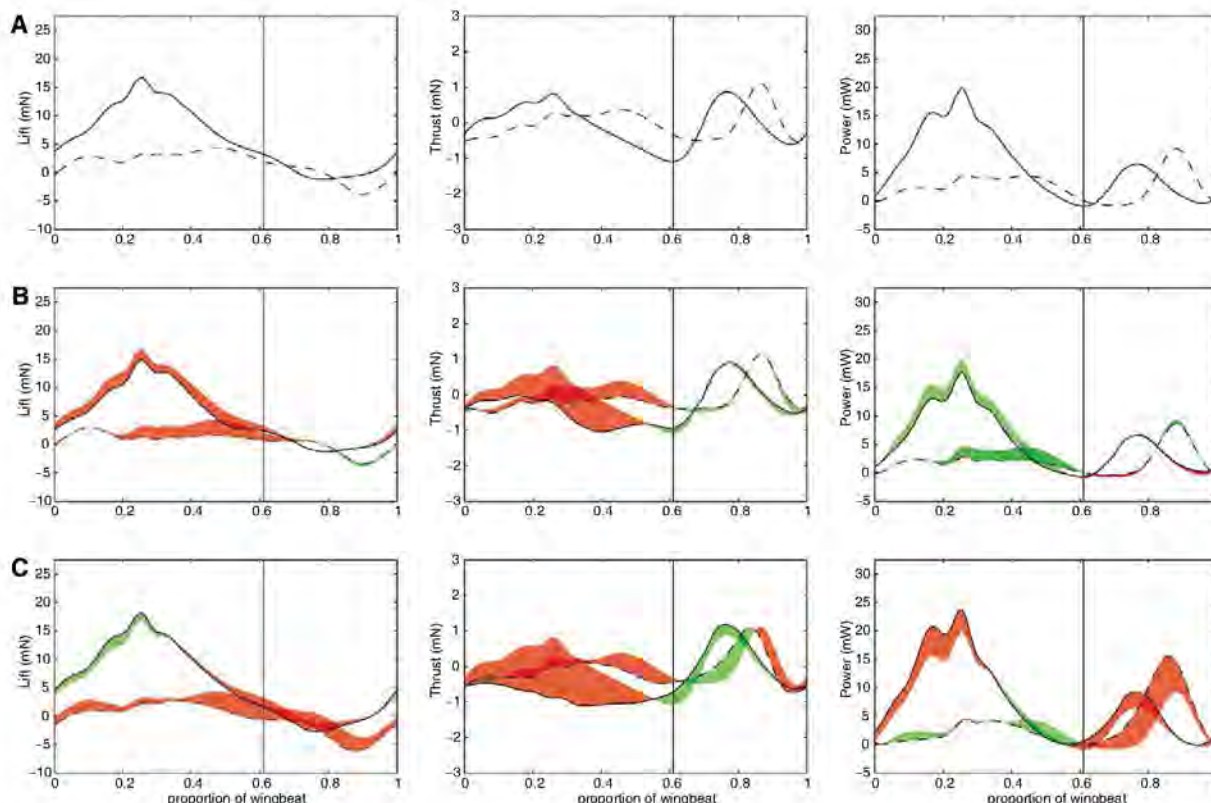
The high-lift aerodynamics of insect flight are typically associated with massive flow separation and large leading-edge vortices (19–21). However, when high lift is not required, attached-flow aerodynamics can offer greater efficiency. The aerodynamic power efficiency of locusts appears to derive from their ability to reduce flow separation and the associated loss of energy as vortical motion in the wake. Simple heaving or flapping flat plates can generate high lift with stable leading-edge vortices (21, 22), but designing robust lightweight wings that can also support efficient attached flow aerodynamics is likely to be much more difficult. Our results show that the secret to doing so lies in building a wing that undergoes appropriate aeroelastic deformation through the course of the wingbeat. We have shown previously that the shape and structure of a locust's hindwing are tuned so that it twists appropriately to maintain a constant angle of attack across the wing during the downstroke (2). Our CFD simulations demonstrate furthermore that time-varying wing twist and camber are essential to the maintenance of attached flow. Implementing such tailored deformations in an engineered system is a difficult problem and may demand an evolutionarily optimized solution in order even to approach the elegance of an insect.

Fig. 3. Computed surface pressure maps from the CFD simulations using full-fidelity kinematics (A), uncambered kinematics (B), and untwisted kinematics (C). The same four consecutive stages of the wingbeat are shown as in Fig. 1, beginning with the start of the downstroke. There is an extensive area of low pressure over the hindwing in the untwisted model, indicative of leading-edge separation. A more limited separation is visible near the root of the hindwing in the uncambered model. There is no clear evidence of separation with the full-fidelity kinematics. The plots at the bottom of the figure show the corresponding 2D flow fields for the stage of the downstroke when the hindwing is horizontal, for the same vertical plane as in Fig. 1. The variation in flow separation between the three kinematics models is demonstrated in these images



by the reversed flow over the top surface of the uncambered and untwisted wings, even though the hindwing angle of attack is identical in all three simulations in these sections. The reduction in the extent of flow separation between the uncambered and untwisted wing must be due to wing twist and associated 3D flow effects. The lack of reversed flows with the full-fidelity kinematics is presumably due to the curvature of the wing section and the reduced local angle of attack at the leading edge. Figure S5 shows the effects on the computed 2D flow field through the wingbeat.

Fig. 4. Instantaneous lift-generated, thrust-generated, and aerodynamic power required in the CFD simulations using full-fidelity kinematics (A), uncambered kinematics (B), and untwisted kinematics (C). Solid and dashed lines denote the lift or power components for the hindwing and forewing, respectively. The wingbeat shown begins at the start of the hindwing downstroke and ends at the point denoted by the vertical line. For the lift and thrust plots, the shading shows the decrement (red) or increment (green) in instantaneous force for the simplified kinematics as compared to the full-fidelity model. For the power plots, the shading shows the equivalent increment (red) or decrement (green) in instantaneous power required.



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Supporting Online Material

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D-Amino Acids Govern Stationary Phase Cell Wall Remodeling in Bacteria

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In all known organisms, amino acids are predominantly thought to be synthesized and used as their L-enantiomers. Here, we found that bacteria produce diverse D-amino acids as well, which accumulate at millimolar concentrations in supernatants of stationary phase cultures. In *Vibrio cholerae*, a dedicated racemase produced D-Met and D-Leu, whereas *Bacillus subtilis* generated D-Tyr and D-Phe. These unusual D-amino acids appear to modulate synthesis of peptidoglycan, a strong and elastic polymer that serves as the stress-bearing component of the bacterial cell wall. D-Amino acids influenced peptidoglycan composition, amount, and strength, both by means of their incorporation into the polymer and by regulating enzymes that synthesize and modify it. Thus, synthesis of D-amino acids may be a common strategy for bacteria to adapt to changing environmental conditions.

In all kingdoms of life, cells predominantly use L-amino acids. In most bacteria, the only D-amino acids produced in significant quantities are D-Ala and D-Glu, which are incorporated

into peptidoglycan (PG) (1). PG is a strong and elastic polymer of the bacterial cell wall that is synthesized and modified by penicillin-binding proteins (PBPs). PG counteracts the cell's osmotic

pressure, maintains cell shape, and anchors components of the cell envelope. The chemistry and structure of PG is dynamic (1, 2), but the factors that regulate alterations in the composition and architecture of PG are not well understood.

Here, we report that a mutant in *Vibrio cholerae* *mrcA*, which encodes a PBPIA homolog (1–2), retained its normal rod shape during exponential growth but became spherical in its stationary phase (Fig. 1A). The mutant's shape change was due to factor(s) that accumulated in the culture media, because exponentially growing rod-shaped *mrcA* cells started to become spherical within 5 min after addition of cell-free supernatants from stationary phase cultures (Fig. 1B). We used the rod-to-sphere shape transition of the *mrcA* mutant as an indicator for such factors and examined their role in the development of PG from wild-type cells.

Stationary phase supernatants were fractionated and assayed for their sphere-inducing activity (3). The active fractions consisted of four amino acids: Met, Leu, Val, and Ile. The D-forms, but not L-forms, of these amino acids stimulated the conversion of *mrcA* rods to spheres (Fig. 1C). A 1.0 mM mixture of these D-amino acids had sphere-inducing activity nearly equivalent to that of unfractionated stationary phase supernatant.

Thus, the absolute stereochemistry at the alpha carbon of these amino acids determines their sphere-inducing activity.

We quantified the D- and L-forms of all amino acids in *V. cholerae* culture supernatants. D-Met and D-Leu were the predominant D-amino acids detected (fig. S1). Total D-amino acid concentrations were low until early stationary phase, then increased for ~8 hours and plateaued at ~1.0 mM (Fig. 2A). Thus, D-amino acid accumulation in stationary phase supernatants could account for sphere-inducing activity. D-Ala was not found in the supernatant, so this normal component of PG is not shed into the media. The abundance of particular D-amino acids, along with the ratios of the enantiomers (fig. S1), suggests a specific mechanism for creating these D-isomers in stationary phase.

Bacteria generate the D-Glu and D-Ala found in PG by specific amino acid racemases, enzymes that convert the chiral carbon of these amino acids from L- to D-forms (4). The *V. cholerae* genome codes for a putative amino acid racemase (*vc1312*), in addition to Glu and Ala racemases. A strain lacking *vc1312* (renamed here *bsrV*, broad-spectrum racemase *Vibrio*) had normal growth and morphology but produced minimal D-Met, D-Leu, D-Val, and D-Ile (Fig. 2B), which suggested that the BsrV racemase generated these four D-amino acids. Notably, BsrV was found in the periplasm (fig. S2), unlike Glu and Ala racemases (4).

Although the morphology of wild-type cells was not altered by D-amino acids (fig. S3), the metabolic expenditure of producing D-amino acids suggested they have important physiological function(s). Because exogenous D-amino acids can influence PG composition and structure (5, 6), we compared PG isolated from wild-type and *bsrV* *V. cholerae*. The *bsrV* mutant contained twice the amount of PG of wild-type cells in stationary phase, whereas PG levels did not differ in exponential phase (Fig. 3A). Addition of physiological amounts of D-Met and D-Leu to *bsrV* cultures

reduced the amount of PG to wild-type levels, which confirmed that the absence of D-amino acids accounted for the increased PG in the *bsrV* mutant. Thus, D-amino acids negatively regulate the amount of PG in stationary phase cells. Moreover, the structure of wild-type and *bsrV* PG isolated from stationary phase cells differed significantly. The glycan chains in stationary phase PG from the *bsrV* mutant were ~80% the length of the wild type; pentapeptides were reduced by ~50%; and there was an increase in trimer muropeptides (table S1). Despite being less abundant, the PG in wild-type cells appeared to be stronger than in *bsrV* cells. Wild-type cells survived 20 times more than *bsrV* cells when subjected to an osmotic challenge (Fig. 3B). Thus, D-amino acid production by BsrV provides a cue for *V. cholerae* to decrease PG synthesis and to alter its cell wall in adaption to stationary phase conditions.

One mechanism by which D-amino acids could alter PG is by incorporation into the polymer. *Escherichia coli* grown in 20 mM D-Met incorporated this amino acid at the fourth position of the PG-peptide bridge (5). High-performance liquid chromatography (HPLC) analyses of PG isolated after the addition of physiologic D-Met (0.5 mM) to exponentially growing *V. cholerae* revealed two peaks that were not detected in control cultures (Fig. 3C and fig. S4, A and C). These peaks correspond to monomer and dimer muropeptides (Fig. 3D) containing D-Met, the same muropeptides observed when 20 mM (or 0.5 mM) D-Met was added to *E. coli* cultures (fig. S4, C and D). Therefore, physiologic production of D-amino acids by *V. cholerae* could influence the PG composition of nearby bacteria of different species. Furthermore, these D-Met-containing muropeptides were present in PG isolated from wild-type, but not *bsrV*, stationary phase cells (Fig. 3C and fig. S4, B and C). About 5% of stationary phase PG contained D-Met modified muropeptides. Thus, physiological production of

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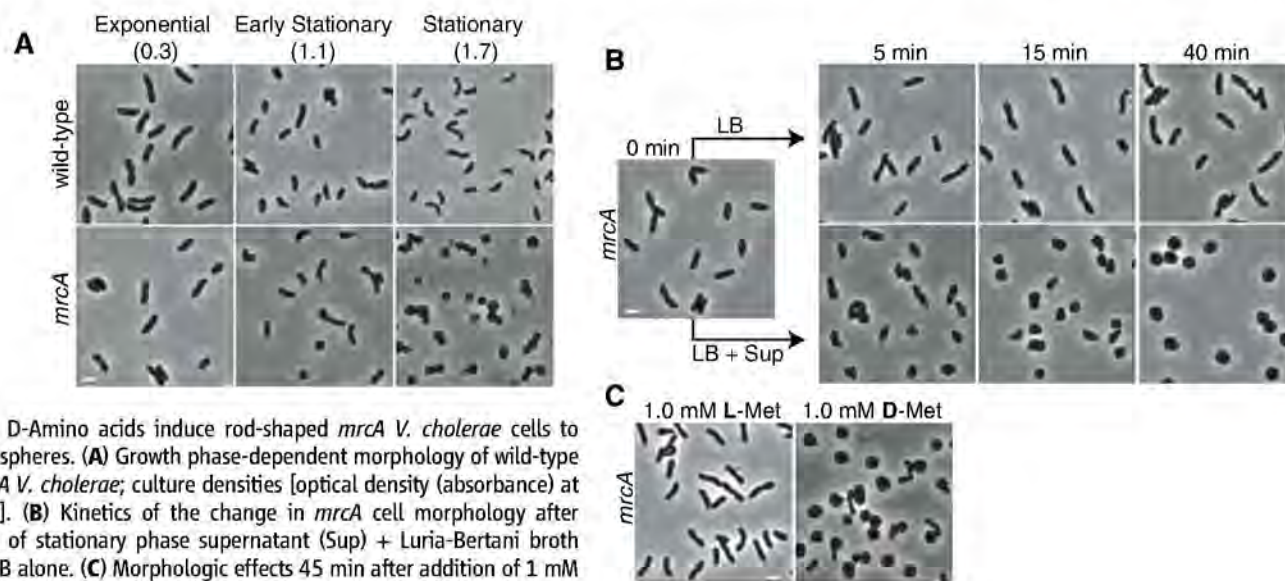


Fig. 1. D-Amino acids induce rod-shaped *mrcA* *V. cholerae* cells to become spheres. (A) Growth phase-dependent morphology of wild-type and *mrcA* *V. cholerae*; culture densities [optical density (absorbance) at 600 nm]. (B) Kinetics of the change in *mrcA* cell morphology after addition of stationary phase supernatant (Sup) + Luria-Bertani broth (LB) or LB alone. (C) Morphologic effects 45 min after addition of 1 mM L-Met or D-Met to rod-shaped *mrcA* cells. Scale bar, 2 μ m.

D-Met by BsrV results in its incorporation into PG in stationary phase. Incorporation of D-Met probably occurs in the periplasm where it is produced, perhaps by means of the activity of a penicillin-insensitive transpeptidase (5, 7), and may directly influence the strength or flexibility of the PG owing to alterations in structure.

D-Amino acids may also have effects on PG that are not a direct consequence of their incorporation. Indeed, 2.0 mM D-Ala stimulated the conversion of rod-shaped *mrcA* mutant cells to spheres, even though D-Ala is already present at the site where D-Met was incorporated (fig. S5). Furthermore, exogenous D-Met (and not L-Met) prevented the binding of Bocillin-FL, a fluorescent penicillin derivative, to several *V. cholerae* cell envelope-associated PBPs, which suggested that D-amino acids directly bound PBPs (fig. S6). Thus, D-amino acids may be regulators, as well as substrates, of the periplasmic enzymes that synthesize and modify PG. Moreover, the periplasmic targeting of BsrV (fig. S2) efficiently links the site of D-amino acid production with the cell wall targets of their action.

Production of D-amino acids was not limited to *V. cholerae*. Diverse bacterial species released D-amino acids (Fig. 4A and table S2). All of these species appear to encode several putative racemases, which suggests that they could produce D-amino acids other than D-Ala and D-Glu (table S3). The particular D-amino acids identified in

stationary phase supernatants varied among bacterial species (Fig. 4A).

We tested if physiological concentrations of D-amino acids also influenced cell wall synthesis in *Bacillus subtilis*, a Gram-positive bacteria that is highly divergent from *V. cholerae*. To monitor synthesis, we used BodipyFL vancomycin (Van-BDP), which labels the cell wall precursor Lipid II (8). In exponential control cells grown in the presence or absence of a mixture of L-amino acids, Van-BDP predominantly stained the septum and the sidewalls in a pattern suggestive of helical and septal PG insertion (8) (Fig. 4, B and C, and fig. S7). In contrast, 30 min after the addition of a mixture of D-amino acids found in stationary phase *B. subtilis* supernatants (table S2), Van-BDP staining of the sidewalls was greatly reduced, which resulted in a pattern similar to that of untreated stationary phase cells (Fig. 4, B and C, and fig. S8). Thus, D-amino acids could down-regulate PG synthesis in stationary phase

B. subtilis, as well as in *V. cholerae*. D-Amino acids released in stationary phase might influence *B. subtilis* PG synthesis by their incorporation into PG (as shown for D-Tyr in fig. S9) and/or by other mechanisms, such as alterations of the activity of *B. subtilis* PBPs. Gross changes in cell morphology occurred when *B. subtilis* was treated with superphysiological concentrations of D-Tyr (fig. S7), reinforcing the idea that D-amino acids regulate cell wall structure. Moreover, addition of the stationary phase D-mixture slowed the growth of exponential *B. subtilis* cultures (9) (fig. S10). Thus, release of D-amino acids by *B. subtilis* during stationary phase may be a mechanism to synchronize growth inhibition and PG synthesis when population density becomes saturating.

Here, D-amino acids were found to be released in stationary phase by diverse bacteria as agents of a process through which cell populations synchronously controlled cell wall assembly and mod-

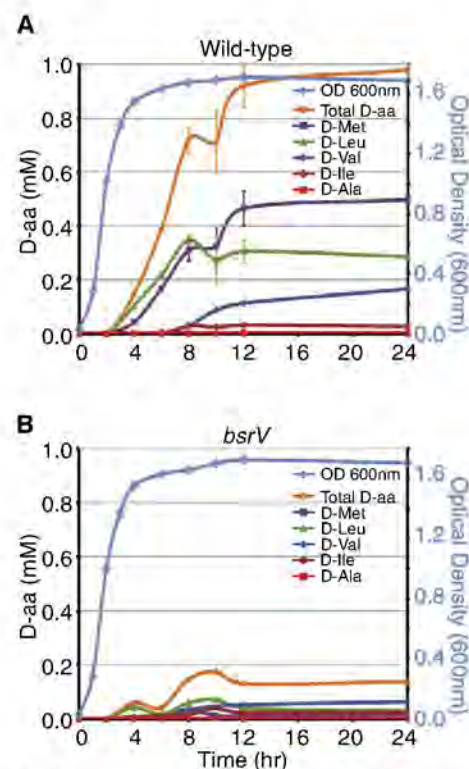


Fig. 2. BsrV is required for production of D-amino acids (D-aa) in *V. cholerae* supernatants. (A and B) Kinetics of the accumulation of the indicated D-amino acids in supernatants from wild-type (A) or *bsrV* (B) *V. cholerae*.

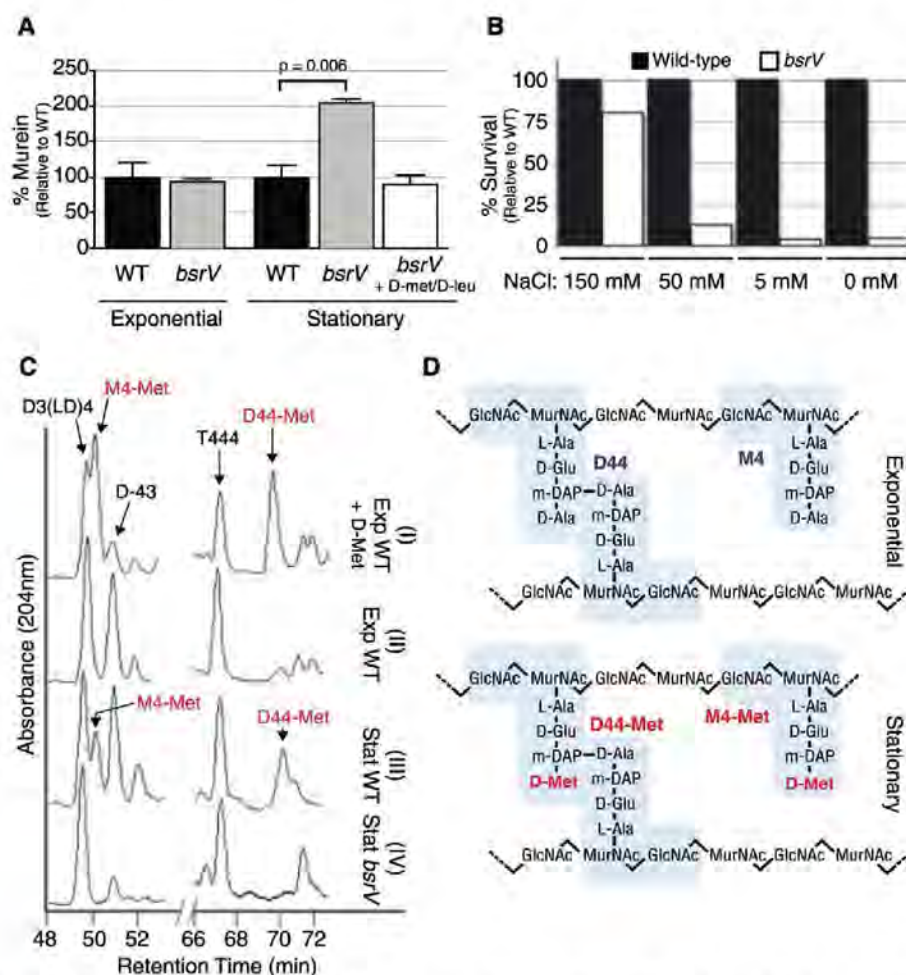


Fig. 3. Influence of D-amino acids on the amount and composition of PG and osmotic tolerance. (A) PG quantification in wild-type or *bsrV* cells grown in LB or LB supplemented with D-Met and D-Leu. Murein (PG) percentage was normalized to wild-type in each growth phase. (B) Recovery of wild-type or *bsrV* *V. cholerae* from media with the indicated concentrations of NaCl. A representative experiment is shown. (C) Portions of the HPLC profiles of muropeptides from exponentially (Exp) growing wild-type cells $\pm$ 0.5 mM D-Met or stationary phase (Stat) wild-type or *bsrV* cells. D-Met-containing peaks are the monomer M4-Met and the dimer D44-Met; their structures are shown schematically in (D). Muropeptide reference peaks: D3(LD)4 [dimer cross-linked at meso-diaminopimelic acid (DAP-DAP)], D-43 [dimer cross-linked at D-Ala-DAP], T444 (trimer cross-linked at D-Ala-DAP and D-Ala-DAP).

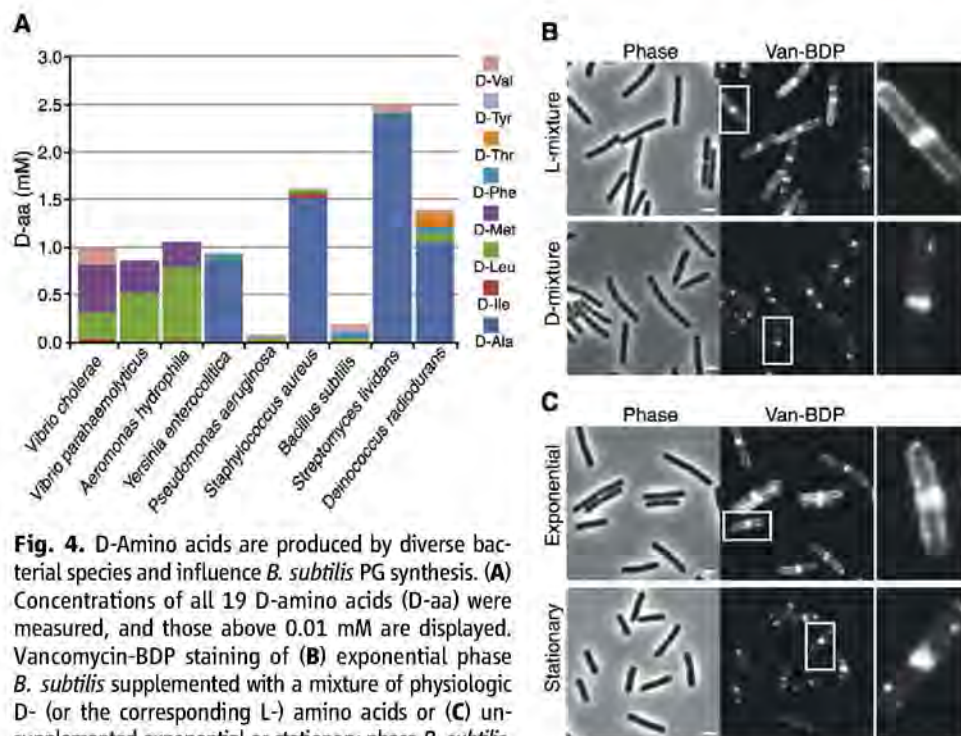


Fig. 4. D-Amino acids are produced by diverse bacterial species and influence *B. subtilis* PG synthesis. (A) Concentrations of all 19 D-amino acids (D-aa) were measured, and those above 0.01 mM are displayed. Vancomycin-BDP staining of (B) exponential phase *B. subtilis* supplemented with a mixture of physiologic D- (or the corresponding L-) amino acids or (C) unsupplemented exponential or stationary phase *B. subtilis*. Scale bar, 2 μ m. Insets are magnified on the right of each corresponding image.

ification. Because the accumulation of D-amino acids coincides with the transition into stationary phase and appears to down-regulate PG synthesis, D-amino acids may enable coordination of metabolic slowing in cell wall and cytoplasmic compartments when resources become scarce. Fur-

thermore, release of D-amino acids may allow for interspecies regulation among bacteria or other organisms that occupy the same niche. D-Amino acids probably affect other aspects of bacterial physiology in addition to those described here. Indeed, D-Ser present in human urine regulates

uropathogenic *E. coli* virulence gene expression (10), and D-amino acids induce sporulation in *Myxococcus xanthus* (11). Thus, bacteria have taken advantage of amino acid chirality to sense and respond to specific environmental conditions.

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Tables S1 to S4

References

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Glucose Deprivation Contributes to the Development of *KRAS* Pathway Mutations in Tumor Cells

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Tumor progression is driven by genetic mutations, but little is known about the environmental conditions that select for these mutations. Studying the transcriptomes of paired colorectal cancer cell lines that differed only in the mutational status of their *KRAS* or *BRAF* genes, we found that *GLUT1*, encoding glucose transporter-1, was one of three genes consistently up-regulated in cells with *KRAS* or *BRAF* mutations. The mutant cells exhibited enhanced glucose uptake and glycolysis and survived in low-glucose conditions, phenotypes that all required *GLUT1* expression. In contrast, when cells with wild-type *KRAS* alleles were subjected to a low-glucose environment, very few cells survived. Most surviving cells expressed high levels of *GLUT1*, and 4% of these survivors had acquired *KRAS* mutations not present in their parents. The glycolysis inhibitor 3-bromopyruvate preferentially suppressed the growth of cells with *KRAS* or *BRAF* mutations. Together, these data suggest that glucose deprivation can drive the acquisition of *KRAS* pathway mutations in human tumors.

Mutations in oncogenes and tumor suppressor genes endow cancer cells with the ability to outgrow their neighboring cells in situ (1). Though numerous studies have

identified the downstream effects of such mutations and their biochemical mediators, relatively little is known about the microenvironmental conditions that provide the selective advantage

that allows cells with such mutations to clonally expand. Mutations in *KRAS* commonly occur in colorectal, pancreatic, and some forms of lung cancer, whereas *BRAF* mutations occur commonly in melanomas, as well as in colorectal tumors without *KRAS* mutations (2–4). *BRAF* and *KRAS* mutations are mutually exclusive; that is, they do not occur in the same tumor, suggesting a common origin and effect. *KRAS* binds to and activates *BRAF*, thereby activating mitogen-activated protein kinase (MAPK) signaling pathways (5, 6). Despite advances in the molecular delineation of the RAS/RAF pathway, the specific environmental pressures that drive *KRAS* and *BRAF* mutations and how *KRAS* and *BRAF* mutations alleviate these pressures are unknown.

To explore this issue, we developed isogenic colorectal cancer (CRC) cell lines in which the endogenous wild-type (WT) or mutant alleles had been inactivated through targeted homologous recombination (figs. S1 and S2 and table S1) (7). We chose to use targeted homologous recombination instead of the more commonly used overexpression or small interfering RNA-dependent systems because only the former permits examination of cells expressing normal or mutant proteins at physiological, normally regulated levels (8). For the investigation of *BRAF*

mutations, we used RKO and VACO432, CRC lines with valine-to-glutamate mutations at codon 600 (V600E) of *BRAF*. This is the most common *BRAF* mutation in human tumors, accounting for more than 90% of *BRAF* mutations (3). To investigate *KRAS* in an analogous manner, we used HCT116 and DLD1, CRC lines with glycine-to-aspartate mutations at codon 13 (G13D). This mutation is one of the most common in CRC, accounting for ~20% of *KRAS* mutations (2). These paired lines essentially differ in only one base pair: the base that is mutated or wild type in *KRAS* or *BRAF*. At least two independent clones of each of the derivatives of each of the four parental cell lines were developed (table S1). In all cases, independent clones with the same genotype behaved similarly in the assays described below.

On the basis of the mutual exclusivity of *KRAS* and *BRAF* mutations and knowledge of the *KRAS* pathway described above, we hypothesized that a common set of transcripts would be deregulated in response to mutations in either gene. We performed expression analysis on clones of various genotypes with microarrays, as well as with massively parallel sequencing of serial analysis of gene expression (SAGE) tags. Only three genes were found to be more than twofold up-regulated in all four lines containing mutant *KRAS* or *BRAF* alleles compared with their isogenic counterparts containing WT alleles: *GLUT1* (also known as *SLC2A1*), *DUSP5*, and *DUSP6* (fig. S3). *DUSP5* and *DUSP6* are known feedback regulators of the MAPK signaling pathway, up-regulated when the pathway is active (9), and thus were unlikely to be positive effectors of *KRAS* and *BRAF* tumorigenesis. On the other hand, *GLUT1* was intriguing, as it encodes a glucose transporter known to be overexpressed in many types of cancer, and its high expression in tumors has been associated with poor prognosis (10, 11). We confirmed the results of the microarray and SAGE expression analyses through quantitative polymerase chain reaction. *GLUT1* transcript expression was always higher, ranging from 3- to 22-fold, in the clones with mutant *KRAS* or *BRAF* alleles compared to the isogenic clones with WT alleles (Fig. 1A and fig. S3). Accordingly, we found that the expression of the

GLUT1 protein was markedly higher in cells with mutant *KRAS* or *BRAF* alleles (Fig. 1B). Targeted disruptions of both alleles of *GLUT1* in RKO and DLD1 cells (fig. S4 and table S1) were used as negative controls to ensure the specificity of the antibodies to *GLUT1* (Fig. 1B). As expected, the *GLUT1* protein was found in the membrane fraction of cells, regardless of *KRAS* or *BRAF* mutational status. Of the 12 human glucose transporter homologs present in the human genome (10), only *GLUT1* was up-regulated in the mutant *KRAS*- or *BRAF*-containing lines compared to those with WT alleles.

To test the specificity of *GLUT1* up-regulation, we evaluated the expression of this protein in cell lines in which the mutant or WT alleles of *PIK3CA* had been disrupted by targeted homologous recombination (12). *PIK3CA* has been implicated in the RAS/RAF pathways, as well as in metabolic regulation, and is commonly mutated in cancers (12, 13). Unlike *KRAS* and *BRAF*, the *PIK3CA* genotype did not have a clear effect on

GLUT1 protein expression (Fig. 1B). We also tested lines with targeted disruptions of both alleles of *HIF1A* (14) (table S1). Though *HIF1A* has been shown to regulate transcription of *GLUT1* in hypoxic conditions (15–17), *GLUT1* expression was found to be largely independent of *HIF1A* status when cells were grown in normal oxygen concentrations (Fig. 1B).

We hypothesized that the up-regulation of *GLUT1* would result in increased glucose uptake in the clones with mutant *KRAS* or *BRAF* alleles. To test this idea, we incubated cells with 2-deoxy-D-[³H] glucose (2-DG), a nonhydrolyzable glucose analog, and measured its uptake. We found that the up-regulation of *GLUT1* was accompanied by a significant increase in glucose uptake in all cells with mutant *KRAS* or *BRAF* alleles compared to the isogenic cells with WT alleles (Fig. 2A). Disruption of *GLUT1* substantially inhibited glucose uptake, demonstrating that *GLUT1* was the major glucose transporter in these cancer cells (Fig. 2A).

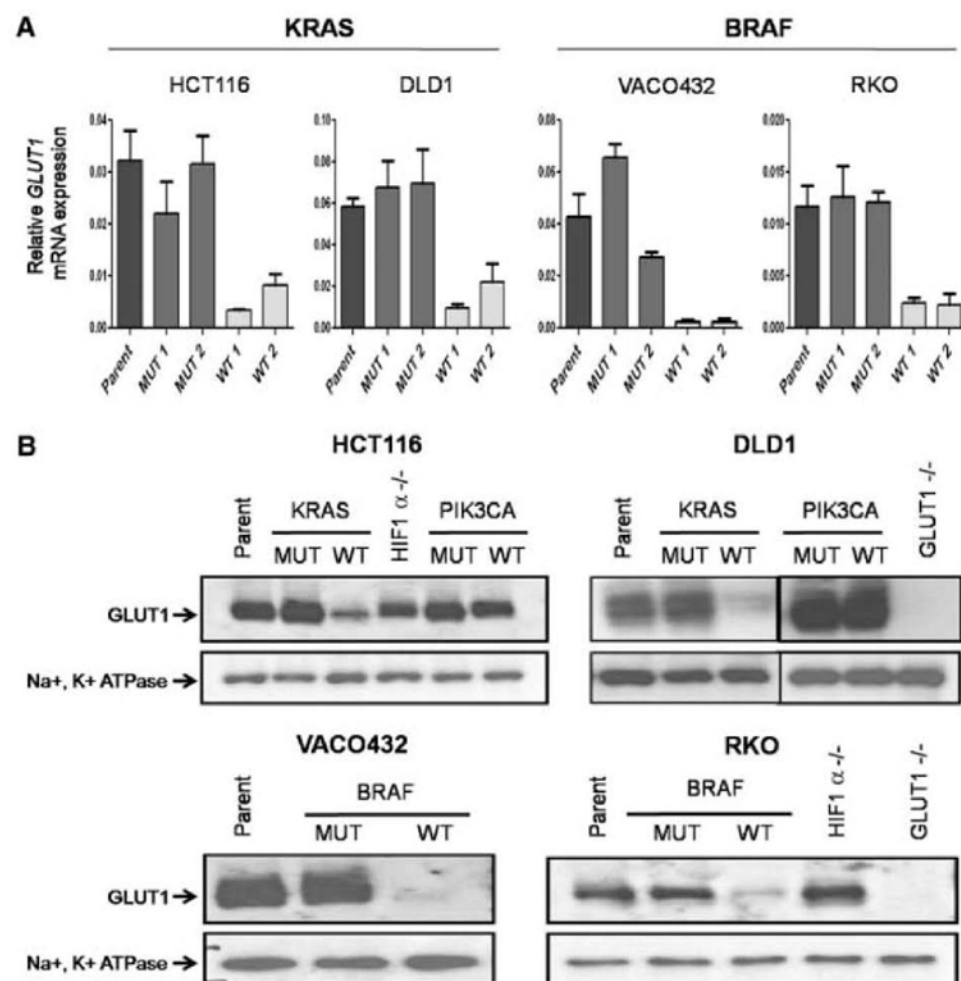


Fig. 1. Expression of *GLUT1* in matched pairs of isogenic clones. **(A)** Expression levels of *GLUT1* transcripts were determined by real-time PCR and normalized to those of β -actin. Each panel includes the parental line (Parent), which harbors both mutant and WT alleles of *KRAS* or *BRAF*, two independent clones with only mutant alleles (MUT1 and MUT2), and two independent clones with only WT alleles (WT1 and WT2). The data represent the mean and SD (error bars) of triplicate experiments. The differences between MUT and WT clones were statistically significant in all cases ($P < 0.05$, Student's t test). **(B)** Expression of *GLUT1* membrane-associated protein levels, as determined by immunoblotting. Na⁺, K⁺-ATPase, a membrane-associated protein, was used as a loading control.

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We next determined whether the increased glucose transport was associated with increased lactate production. Lactate production was significantly increased in cells with mutant *KRAS* or *BRAF* alleles, indicating an increased rate of glycolysis and consistent with higher glucose uptake (Fig. 2B). Lactate production was very low in cells without *GLUT1* genes, as would be expected if *GLUT1* functions as the major glucose transporter in these cells (Fig. 2B). On the other hand, oxygen consumption in cells with mutant *KRAS* or *BRAF* alleles was similar to that in cells with WT alleles of these genes, suggesting that mitochondrial function and oxidative respiration were not affected by *KRAS* or *BRAF* mutation (fig. S5). Accordingly, there were no consistent differences in cellular adenosine triphosphate (ATP) concentrations or ATP/ADP (adenosine diphosphate) ratios in cells with mutant *KRAS* or *BRAF* alleles compared with their WT counterparts (figs. S6 and S7).

These results suggested that the increase in glucose uptake and glycolysis might provide a growth advantage to cells with *KRAS* or *BRAF* mutations in low-glucose environments. When grown in standard, commercially available media (25 mM glucose), all cell lines, including those without the *GLUT1* gene, grew reasonably well (fig. S8) and formed colonies when plated at low density. However, when placed in media containing low-glucose concentrations (0.5 mM), only cell lines with *KRAS* or *BRAF* mutant alleles sur-

vived (Fig. 3A). This growth was dependent on *GLUT1*, as cells in which the *GLUT1* gene was inactivated by targeted homologous recombination lost their ability to form colonies in low-glucose environments, even though they contained mutant *KRAS* or *BRAF* genes (Fig. 3A). In contrast, such growth was independent of *HIF1A*, as cells with mutant *KRAS* or *BRAF* alleles survived in low-glucose conditions when the *HIF1A* gene was inactivated by targeted homologous recombination (Fig. 3A).

We then determined whether clones with mutant *KRAS* or *BRAF* genes could selectively outgrow cells without these mutations. For this purpose, cells with mutant *KRAS* or *BRAF* alleles were mixed with an excess of cells containing WT *KRAS* or *BRAF* alleles, respectively, and were incubated in either low (0.5 mM) or standard (25 mM) concentrations of glucose. Cells with mutant *KRAS* or *BRAF* alleles preferentially survived in low-glucose conditions and overtook the population within two weeks after the medium was changed to one containing 25 mM glucose. In contrast, the cells with WT alleles remained predominant when they were not exposed to low-glucose conditions (Fig. 3B).

To mimic situations that might occur in vivo, we subjected cells with only WT alleles (obtained by disrupting the mutant *KRAS* or *BRAF* alleles) (figs. S1 and S2) to a low-glucose environment in vitro and isolated the few colonies that survived

(fig. S10). We reasoned that in the ~35 generations that had elapsed between targeted disruption and this experiment, a small fraction of cells would have spontaneously acquired mutations in genes that could potentially permit them to survive in medium containing low-glucose concentrations. The fact that the two cell lines used for this experiment were both mismatch-repair deficient should have facilitated the development of such de novo mutations (18). We found that the fraction of DLD1 *KRAS* (-/+) or RKO *BRAF* (-/+) cells that could form colonies in low-glucose conditions was ~0.05%. Once formed, the colonies were grown in a medium containing standard concentrations of glucose (25 mM). We found that more than 75% of the clones derived from either cell line after selection in low-glucose, stably expressed high levels of *GLUT1* protein, even when subsequently grown in standard medium (25 mM glucose) (Fig. 3C and fig. S11). Thus, the selection for growth in low-glucose conditions resulted in a permanent up-regulation of *GLUT1* expression in the majority of clones that survived, and this up-regulation persisted after normoglycemia was reinstituted, indicating a heritable change. Control clones derived analogously but, with 25 mM glucose substituted for 0.5 mM glucose during the selection period, did not show elevated *GLUT1* expression (Fig. 3C and fig. S11). When the clones derived from DLD1 *KRAS* (-/+) cells were assessed for mutations, 4.4% of the clones arising under hypoglycemic conditions had mutations in *KRAS* (73.5% of these had G12D, 25.2% had G13D, 1.3% had G13C, and 0% had *BRAF* V600E or other mutations in *KRAS* at codon 12 or 13). No *KRAS* or *BRAF* mutations were identified in 2000 DLD1 *KRAS* (-/+) clones generated in the presence of standard concentrations of glucose ($P < 0.000001$, χ^2). In the clones derived from RKO *BRAF* (-/+) cells, 0.8% of the clones surviving low-glucose exposure had a G12D *KRAS* mutation, whereas none of 2000 clones grown in the presence of standard glucose concentrations had such mutations ($P < 0.01$, χ^2).

We next attempted to exploit this phenotype to specifically target cancer cells with *KRAS* or *BRAF* mutations. We reasoned that cells with *KRAS* or *BRAF* mutations had stably reprogrammed their metabolic pathways and might be dependent on glycolysis for growth. Accordingly, an agent such as 3-bromopyruvate (3-BrPA), which inhibits glucose metabolism through inhibition of hexokinase (19), might be selectively toxic to cells with *KRAS* or *BRAF* mutations. When we tested this hypothesis using the paired isogenic cell lines, we found that 3-BrPA was highly toxic to HCT116, DLD1, VACO432, and RKO cells with *KRAS* or *BRAF* mutations but was much less toxic to the matched cell lines lacking *KRAS* or *BRAF* mutant alleles (Fig. 4A).

We next explored whether this approach might be applicable to experimental tumors in mice. As a prelude, we found that cells with disrupted mutant *KRAS* (20) or *BRAF* alleles grew

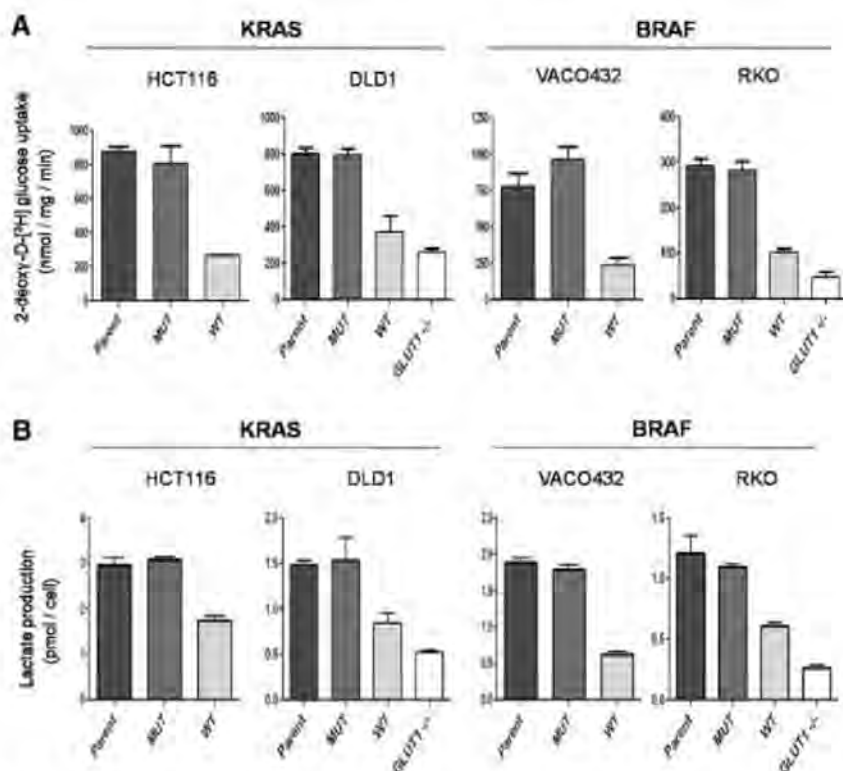


Fig. 2. Glucose uptake and lactate production in cells with *KRAS* or *BRAF* mutations. **(A)** Glucose uptake, as determined with the use of [3 H] 2-deoxyglucose, was normalized to the amount of total protein. Differences between MUT and WT clones were statistically significant ($P < 0.01$, Student's *t* test). **(B)** Lactate production was normalized to cell number. The differences between MUT and WT clones were statistically significant in all cases ($P < 0.03$, Student's *t* test). The data represent the mean and SD (error bars) of triplicate experiments.

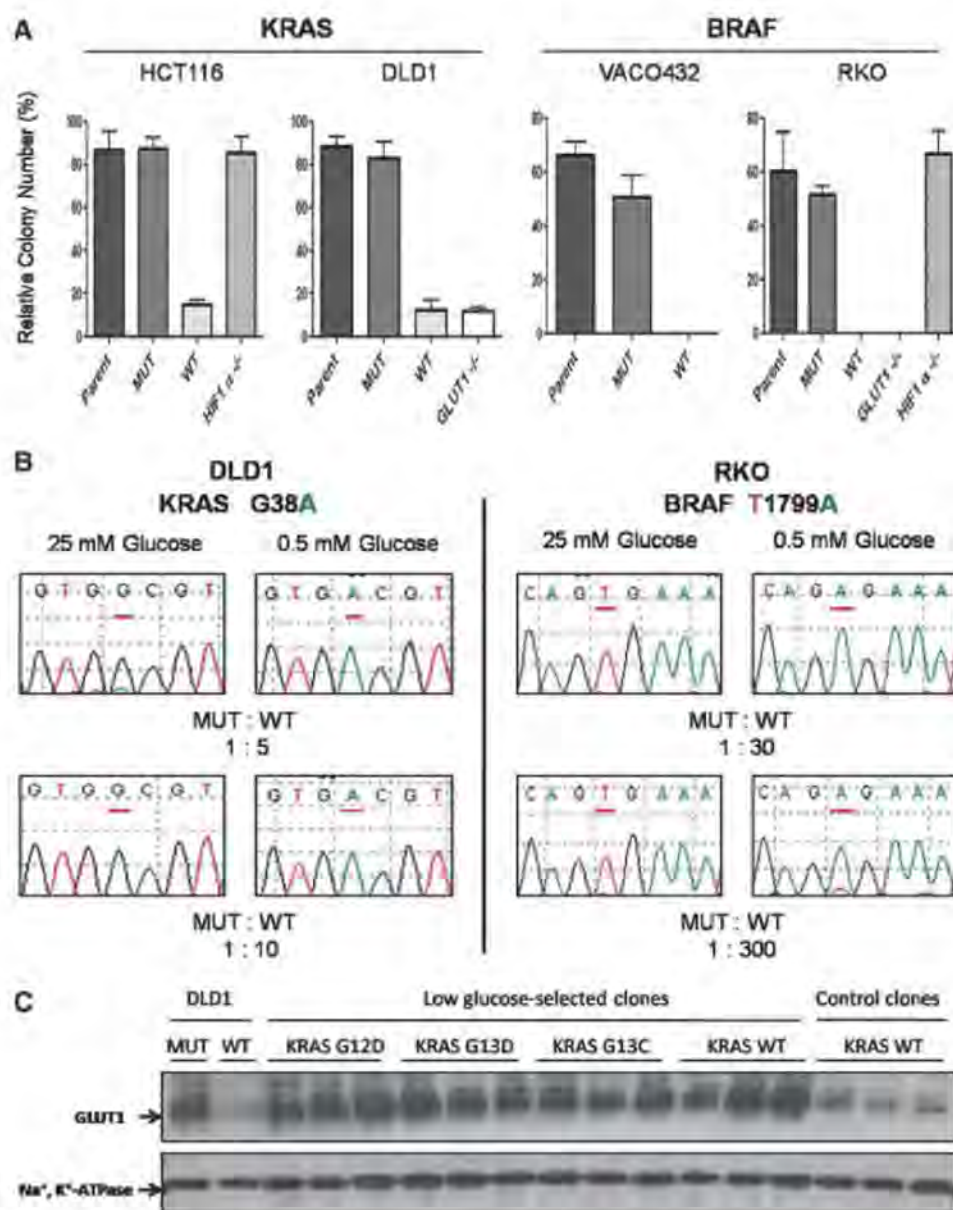


Fig. 3. *KRAS* and *BRAF* mutations confer a selective growth advantage in hypoglycemic conditions. (A) Cells were subjected to a low-glucose environment (0.5 mM) for 2 (RKO and VACO432) or 4 (HCT116 and DLD1) days, then dissociated and plated in media containing standard concentrations of glucose (25 mM). Colony counts were normalized to those obtained in cells subjected to the same experimental procedure, with the exception that standard glucose levels were substituted for low-glucose levels. See (7) for details. The differences between MUT and WT clones were statistically significant in all cases ($P < 0.004$, Student's t test). Error bars indicate SD. **(B)** MUT and WT clones were mixed at the indicated ratios and grown in media with 0.5 mM glucose for 2 (RKO) or 5 (DLD1) days. The media was replaced with one containing 25 mM glucose, and the cells were incubated for another 10 to 16 days. RNA was purified from the cells that survived, and the *KRAS* or *BRAF* genes were PCR-amplified and sequenced. G and A nucleotides at the underlined positions in the sequencing chromatograms represent WT and mutant alleles of *KRAS*, respectively, in DLD1 cells. T and A nucleotides represent WT and mutant alleles of *BRAF*, respectively, in RKO cells. **(C)** DLD1 cells in which the mutant *KRAS* allele had been deleted by targeted recombination [*KRAS* (-/+)] were plated in low-glucose conditions (0.5 mM). After 25 to 30 days, the few clones that survived were grown in standard glucose (25 mM) conditions and assessed for GLUT1 expression and the sequence of the *KRAS* gene. Clones that harbored mutant alleles of *KRAS* (G12D, G13D, or G13C) are indicated, as are clones in which *KRAS* remained as wild type. As controls, the same cells [*KRAS* (-/+)] were plated at limiting dilution in media containing 25 mM glucose and individual clones assessed for GLUT1 expression (Control clones). The parental cells used for these experiments (DLD1, WT) are also included, as were their isogenic counterparts in which the WT rather than the mutant allele was disrupted by homologous recombination (DLD1, MUT). All clones had been growing in media containing 25 mM glucose for at least 20 days when harvested for the assessment of GLUT1 expression by immunoblotting. Na⁺, K⁺-ATPase was used as a loading control. A diagram of the selection scheme is provided in fig. S10, and detailed methods are provided in (7).

poorly as xenografts in nude mice compared with their isogenic counterparts with mutant alleles (fig. S12). DLD1 and RKO cells in which the *GLUT1* gene was disrupted also grew poorly in nude mice, even though these cells contained mutant *KRAS* and *BRAF* alleles, respectively (fig. S12). These results suggest that the micro-environment in xenografts mimics the low-glucose environment in vitro and provides a reasonable system in which to test the effects of glycolytic inhibitors. 3-BrPA significantly inhibited the growth of established xenografts derived from HCT116 and VACO432 cells (Fig. 4B). These results provide proof of principle that glycolytic inhibitors can retard tumor growth at doses that are nontoxic to normal tissues in vivo.

Our results led us to investigate glucose metabolism in a completely unbiased way, complementing previous work by other investigators. A role for metabolic abnormalities in cancer has become increasingly recognized (21, 22). These metabolic abnormalities often appear to involve abnormal glycolysis, as first demonstrated decades ago by Warburg (23). Insightful hypotheses about the manifold ways in which such metabolic abnormalities can promote tumor progression have been described (24–26). It has also been demonstrated that transformation of rodent fibroblasts by several oncogenes, including *HRAS*, can up-regulate glucose transporter expression (16, 27–29). However, because transformation by overexpressed oncogenes affects the expression of hundreds of genes and dramatically alters the phenotype of rodent fibroblasts, the relation between increased glucose transporter expression and tumorigenesis was not clear. In human tumor cells, no obvious relation between *GLUT1* and *RAS* mutations has been identified (30, 31). Moreover, in many previous experimental studies in rodent cells, the increased *GLUT1* expression was ascribed to induction of HIF1A and linked to hypoxia (15, 16, 32, 33). Our results show that the increased *GLUT1* transcription was unrelated to HIF1A, because genetic disruption of the *HIF1A* gene did not affect the expression of *GLUT1*, nor did it affect survival under hypoglycemic conditions. Cells without mutant *KRAS* or *BRAF* alleles were remarkably sensitive to hypoglycemia, but not to hypoxia (Fig. 3 and fig. S9). Furthermore, the changes in *GLUT1* expression and resultant metabolic changes in human CRC cells were stable phenotypes rather than transient responses to low-glucose levels, as they persisted under normoglycemic conditions. This stability is consistent with them being the consequence of specific genetic mutations, such as those in *KRAS* or *BRAF*. In aggregate, our results suggest that low-glucose environments are a driving force underlying the development of *KRAS* and *BRAF* mutations during tumorigenesis.

F-18-Fluoro-deoxyglucose (FDG)-positron emission tomography (PET) scans are routinely used to image cancers in the clinic. Positive signals in cancers are the result of increased glucose

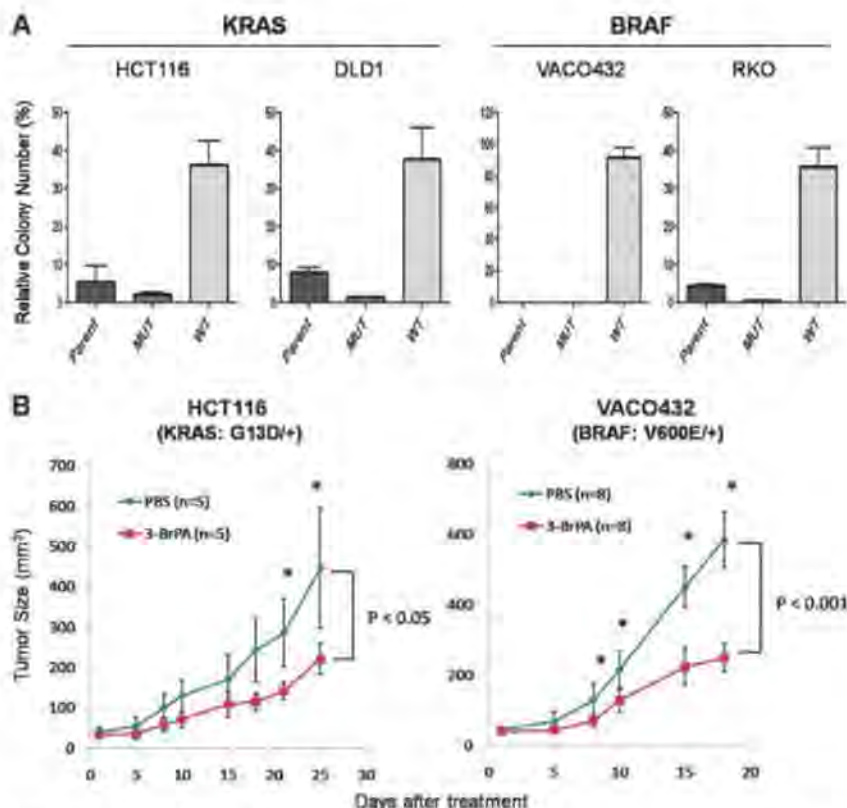


Fig. 4. The glycolysis inhibitor 3-BrPA is selectively toxic to cells with mutant *KRAS* or *BRAF* alleles. **(A)** Colony formation was assessed after 3-BrPA treatment (110 μ M) for 3 days. Colony counts were normalized to those obtained from cells subjected to the same procedure without exposure to 3-BrPA. The differences between MUT and WT clones were statistically significant in all cases ($P < 0.008$, Student's *t* test). Error bars indicate SD. **(B)** Mice with subcutaneous tumors established from HCT116 (*KRAS*: G13D/+) or VACO432 (*BRAF*: V600E/+) cells were injected intraperitoneally with 3-BrPA or phosphate buffered saline (PBS) daily for 2 weeks. *n* represents the number of mice used in each group. Data points and error bars represent the means and SD for each group of mice. Asterisks denote times when there were significant differences between the tumor sizes in the PBS versus 3-BrPA groups ($P < 0.05$, Student's *t* test).

transporter expression or glucose uptake (34). Our data showed that in four different human cancer cell lines, an increase in *GLUT1* expression and glucose uptake was critically dependent on *KRAS* or *BRAF* mutations. It is interesting that abnormal FDG-PET signals can be observed in progressing pre-malignant colorectal neoplasms (adenomas) congruent with the time during tumorigenesis in which *KRAS* or *BRAF* mutations appear (35, 36).

Our results raise a variety of questions. One concerns the relation between hypoxia and hypoglycemia. Though both of these deficiencies are likely to be encountered in tumor microenvironments, it is possible that each condition sets the stage for the selection of particular genetic abnormalities (24). For example, hypoglycemic conditions favor the selection of cells with *KRAS* or *BRAF* mutations, whereas hypoxic conditions may favor the selection of cells with *PIK3CA*, *CMYC*, or *TP53* mutations (21, 37). Another question addresses why 90% of CRCs exhibit high FDG-PET signals and *GLUT1* expression

(35, 38, 39), whereas *KRAS* or *BRAF* mutations are only observed in ~50% of such cancers (4). One possible explanation is that other genetic alterations that affect the same pathway can substitute for *KRAS* and *BRAF* mutations in up-regulating *GLUT1*. This idea is consistent with recent data indicating that the same pathway can be mutationally activated through disparate mutations in numerous genes (1, 40, 41). It is also consistent with our in vitro selection experiments. Though the majority of clones that survived hypoglycemia up-regulated *GLUT1*, only a minority of these clones had acquired *KRAS* or *BRAF* mutations.

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Supporting Online Material

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Materials and Methods

Figs. S1 to S12

Table S1

References

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WHO NEEDS LABELS?

MACROMOLECULAR INTERACTION SANS LABELS

When it comes to monitoring biological interactions, whether of nucleic acids, proteins, small molecules, or cells, labels are essential for detection, right? Researchers certainly have embraced detection modalities based on tagging with radioisotopes, fluorescent dyes, and conjugated enzymes. Yet in many cases such molecular baggage is unnecessary, and possibly detrimental. But there is another way. Whether based on optical, mechanical, or electrical detection, label-free methods can probe molecular pas de deux in their native, unadulterated states. As a result, they are faster, simpler, and more physiological than their labeled counterparts. **By Jeffrey M. Perkel**

The research community is taking note. Says Guenter Gauglitz, whose lab does extensive work in this area, when asked why researchers should eschew tried-and-tested label-based methods for label-free: “I would pose the question the opposite way: Why bother with labeled methods?”

Tagging methods, says Gauglitz, of the **University of Tübingen**, Germany, have one very obvious disadvantage: “You have to label the systems.” That, in turn, can impact the “bioactivity” of the labeled molecule, for instance through misfolding, reduced mobility, or steric hindrance. Labeling reagents are also pricey, may tag different molecules with varying efficiency, and in some cases are incompatible with live cells.

Label-free approaches, in contrast, reduce biomolecular interactions to their most essential components: molecule A, molecule B, and a detection scheme to watch them in action, often in real time.

Researchers have, to some extent, caught on, but not in droves. “To date it’s been a niche technology,” says Matthew Cooper of the **University of Queensland**, Australia, editor of the recently published book *Label-Free Biosensors: Techniques and Applications* (Cambridge University Press, 2009). “It’s been a classic early-adopter play.”

Pharmaceutical companies have been more enthusiastic, pressing label-free systems into service for fragment-based screening, lead optimization, and affinity ranking, among other applications.

At biopharmaceutical firm **Amgen**, as head of the company’s protein-protein interaction group, principal scientist Ching Chen uses three different label-free platforms. Those systems, from **GE Healthcare**, **ForteBio**, and **Sapidyne Instruments**, are used, she says, “in a complementary way,” for such applications as primary screening, epitope mapping, and affinity determination.

Label-free technologies provide “a much more straightforward answer [than labeled approaches],” she says. “They provide much better confidence when interpreting the data and give us confidence and speed in the selection of molecules.”

Three Essentials

All label-free (and for that matter, labeled) technologies, regardless of their operating principle and configuration, have at their heart three fundamental components, says Cooper: a receptor, a transducer, and an analyzer.

The receptor, of course, is what makes a biosensor, a biosensor—it specifically captures the molecule, cell, or pathogen of interest from a biological fluid or sample. The transducer, says Cooper, is the “detection modality, what converts that biological event into a photometric, electrochemical, electrical, or acoustic change.” That change, which is proportional to the extent of binding, is then quantified by the analyzer.

Observe how these pieces work together in one of the most popular label-free approaches, surface plasmon resonance (SPR). [continued >](#)



“Label-free technologies provide “a much more straightforward answer” [than labeled approaches].”

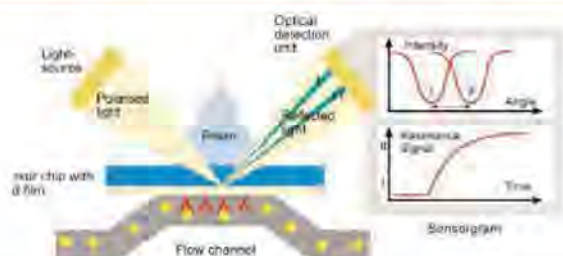
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Proteomics



As implemented by GE Healthcare, an SPR biosensor comprises a thin gold film (about 50 nm thick) mounted on the flat face of a prism. On the side of the gold film facing away from the prism is a surface on which capture molecules (such as antibodies or DNA) are immobilized. This surface (the transducer) is exposed to a fluidics interface, such that reagents—whether capture molecules, analytes, or buffer—can flow over and interact with the biosensor surface (see figure above).

Within the instrument itself, the biosensor, light source, and detector form the vertices of a triangle, an arrangement called the Kretschmann configuration. As polarized light passes through the prism at an angle, it strikes the gold and reflects back through the prism at the “specular” angle—that is, as if the gold were a mirror. For the most part, the gold really is a mirror, and over a wide range of wavelengths (or angles), the light hitting the detector (a photodiode that measures light intensity) is 100 percent of that which left the source. But at one particular combination of wavelength and angle, reflection drops nearly to zero—a phenomenon called the “SPR dip” or “SPR resonance.”

That’s because under those precise conditions, “the light resonantly couples with the conduction electrons near the surface of the gold film to create clouds of oscillating electrons called a surface plasmon,” says Charlie Campbell, the West Professor of Chemistry at the University of Washington. “When in resonance, the momentum of this plasmon parallel to the surface matches the parallel momentum of the incoming light; since the latter is a function of the refractive index of the material under analysis in contact with the gold surface, the angle [at fixed wavelength] or wavelength [at fixed angle] of the dip can be used to monitor the refractive index of that material.”

In practice, this index of refraction varies ever so slightly as molecules bind to the sensor surface. So as intermolecular binding events unfold, the wavelength at which the SPR “dip” occurs will change, and the magnitude of that change is a function of the extent of binding.

The “refractive index change is directly proportional to the mass change,” says Stefan Lofas, principal scientist for the Biacore line at GE Healthcare Life Sciences. “So actually, you can say that we quantitatively measure the change in mass when something binds to the surface.”

And, because SPR devices are often coupled to flow cells that can deliver analytes or buffer, they can measure those events in real-time (in contrast to systems such as ELISA, which collect end-point measurements). That makes SPR systems particularly useful for collecting kinetics data—and explains their popularity in the pharmaceutical industry as well.

Biopharmaceutical firm Xencor runs its Biacore 3000 “24/7” in its antibody development pipeline, says John Desjarlais, vice president of research; MedImmune’s SPR instruments (from Biacore and Bio-Rad) have been used for affinity kinetic characterization, epitope competition studies, and characterizing concurrent binding of

multispecific antibodies, says Herren Wu, vice president of research and development.

“In the past 10 years, almost all compounds have gone through the Biacore measurement,” he says.

By all accounts, Biacore has been a dominant force in the label-free market in general and SPR in particular for nearly two decades. “Last fall, we celebrated the 10,000th publication with Biacore-related data,” Lofas says. Yet competition is growing. Bio-Rad’s ProteOn system can measure 36 interactions simultaneously via a criss-crossing array of 6x6 fluidic channels, while Fujifilm Life Science’s AP-3000 can probe six targets at once. An in-development system from Plexera, on the other hand, applies an SPR variant called imaging SPR (or SPR microscopy) to monitor interactions on arrays of up to several thousand spots by imaging light intensity using CCD cameras.

Yet all these techniques suffer from the same basic shortcomings, namely, that they are flow-based and mounted on a prism. As a result, SPR is generally incompatible with standard microtiter-plate formats, including much of the high throughput drug discovery workflow.

Optical Alternatives

Several companies have overcome this problem by devising SPR alternatives in standard microplate labware. Though flow-based systems have the advantage of providing kinetics data, microplate-based systems can accommodate a wider variety of sample types, from cruder samples that would gum up microfluidic channels, to live cells that are currently too large for them.

The majority of these options—like SPR—rely on evanescent waves. As described in a review by Cooper in *Nature Reviews Drug Discovery* (1:515, 2002), the “evanescent wave phenomenon” occurs when “total internal reflection of light at a surface–solution interface produces an electromagnetic field, or evanescent wave, that extends a short distance (~100–200 nm) into the solution.” That wave effectively probes the interface—and is in turn “tuned” by it in a dose-dependent fashion—allowing detection.

Just how that detection occurs depends on what aspect of the outbound light the detector looks at. Corning’s Epic system probes the index of refraction on its biosensor surface using a “resonant waveguide grating structure,” says Mark Krol, technology manager at Corning.

“From a phenomenological standpoint, [Epic] is very similar to SPR, but the optical physics are very different,” Krol explains.

As with SPR, molecular interaction events on the sensor surface change its index of refraction. But rather than monitoring the SPR dip, Epic scans for a concomitant change in reflected wavelength, whose magnitude is a function of the degree of binding.

SRU Biosystems’ BIND performs a similar measurement using an optical device called a photonic crystal.

“A photonic crystal is just a fancy way of saying we have a material with two different refractive indexes in it, a high refractive index and a low refractive index, that alternate from high to low to high to low in a periodic fashion,” explains company co-founder Brian Cunningham of the University of Illinois, Urbana-Champaign.

In this case, the crystal is illuminated with near-infrared light, almost all of which passes through the sensor. But one wavelength resonates with the crystal and is reflected back. “At that one wavelength, the resonant wavelength, the photonic crystal structure acts as a perfect mirror,” Cunningham explains. “So it reflects very efficiently at that one wavelength, and all other wavelengths pass through.” When a biomolecular interaction occurs on the sensor surface, that wavelength shifts, producing a measurable readout. *continued >*



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Cunningham compares the effect to a guitar string. "If you strum it, you get a certain wavelength out in terms of the sound it makes," he says. "If you paint the string and strum it again, you will get a different resonance, a different sound. In the same way, when mass is added to this sensor, it reflects the light at a different wavelength."

Maven Biotechnologies' in-development Polaron instrument measures changes in light polarization, says chief scientific officer Shane Dultz. Based on a technology called LFIRE (label-free internal reflection ellipsometry), Polaron's is an imaging approach that measures changes in the elliptical polarization of light as it interacts with the sensor surface to chronicle biomolecular interactions in miniaturized protein microarrays.

"It turns out that the phase shift, or the degree to which the light's elliptical polarization is changing, is proportional to the number of molecules per square micron on that surface," Dultz says.

Though still in development, Polaron will image arrays in the bottom of 96-well glass bottom plates, Dultz says, with up to 700 protein spots per well. Each spot, he adds, can be analyzed either continuously or on an endpoint basis.

Silicon Kinetics (SKi Pro system), **BiOptix**, and **ForteBio** (Octet) employ an alternative strategy called interferometry. Used, among other things, to calculate the distance to astronomic objects, interferometry may also be used to measure the thickness of the molecular layer on the biosensor surface as biochemical events occur.

In ForteBio's case, the biosensor is a narrow tube (or fiber tip) with two parallel surfaces perpendicular to its long axis: an invariant reference surface and a sensor surface, to which capture molecules (such as antibodies) are bound. When light is directed down the barrel of the tube, it bounces off both surfaces on its way back to

the detector, producing a composite signal that is a reflection of both waves.

"The two reflections interfere constructively and destructively and there is a net signal seen at the detector," explains Sriram Kumaraswamy, product manager of ForteBio.

As molecules bind to the biosensor surface, that net signal pattern changes, producing a difference in the resulting spectrum whose magnitude depends on the size and number of molecules bound.

Electrical and Mechanical Biosensing

Though most commercial systems employ optical detection, there are other ways to detect interactions sans labels. As Cunningham puts it, "All optical biosensors take advantage of the fact that biomolecules all have a dielectric coefficient or refractive index that is higher than that of water. But what other properties does a molecule have?"

One property, of course, is mass, and several mechanical approaches exist to probe that, says Rashid Bashir, the Bliss Professor of Electrical and Computer Engineering and Bioengineering at the University of Illinois at Urbana-Champaign. One such approach is "resonance mass sensing."

Many structures—quartz crystals, for instance—have a characteristic vibrational frequency, Bashir explains. Because that frequency depends on mass, if the device is small enough, "as I add a mass to it, I can detect that added mass by the change in the resonant frequency of the resonator."

TTP LabTech's RAPid 4 system is a quartz crystal microbalance device based on this principle.

An alternative strategy, stress sensing, uses mechanical stress to follow biochemical events on the surface of, for instance, a cantilever (a kind of nanoscale diving board). "If you perform a biochemical reaction on only one surface of these cantilevers, then that change in the local surface energy will result in a change in surface stress, and the cantilever will actually bend," Bashir explains. As with other label-free methods, the degree of that flexion depends on the extent of macromolecular interaction, and can be quantified by bouncing a laser off the cantilever's tip.

Others have devised label-free sensing methods based on electronic fluctuations resulting from macromolecular interactions. According to Bashir, systems have been devised based on impedance or electrochemical sensing using electrodes in fluid or potentiometric sensing using field-effect transistors or silicon nanowires. **Acea Biosciences** and **MDS Analytical Technologies** have commercialized electrical impedance-based systems, which measure changes in current flow between electrodes when cells deposited between the electrodes change shape, adherence, or mass distribution as a result of, for instance, G protein-coupled receptor stimulation.

Ultimately each strategy, whether optical, mechanical, or electrical, has its pros and cons. SPR, for instance, has decades of user know-how behind it. Electrical approaches may be most amenable to miniaturization, says Bashir, as they require neither optics nor vibrational detectors, whereas electrical and mechanical strategies have the advantage of being immune to optical distortions at the biosensor surface.

Whichever molecular property you focus on, once you get over the learning curve, you might find that once you go label-free, there's no going back.

Jeffrey M. Perkel is a freelance science writer based in Pocatello, Idaho.

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For information 617-494-9794

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bel-free Dip and Read biosensor assays in high throughput mode, while speeding the time to results for kinetic characterization and quantitation measurements. The systems support two 384-well or 96-well plate positions. A full complement of samples can be run in one plate, while the second plate holds buffers, diluents, and controls.

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AMS Biotechnology

For information +44-1235-828200

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Keystone Symposia on Molecular and Cellular Biology is seeking an International Development Specialist to work full-time on fundraising for conferences held outside of North America. Keystone Symposia is a 501(c)(3) nonprofit, educational organization that plans and conducts 50-60 scientific conferences annually. Since its inception in 1972, the organization has convened symposia on life science topics primarily in North America, but starting in 2005 with a conference in Singapore, Keystone Symposia began to expand globally. Global conferences are planned, or have recently taken place in England, Ireland, Austria, Thailand, China, Australia, South Africa, Uganda, Tanzania, and Japan. Looking forward, Keystone Symposia's Board of Directors and Management are committed to a robust globalization strategy that promotes opportunity and participation of scientists worldwide in the highest-quality international conferences. Priorities for the organization are connecting scientists with diverse research interests; catalyzing scientific collaboration; developing scientific talent worldwide; and accelerating life science discoveries that benefit the world.

The successful candidate will report to the Chief Executive Officer and work closely with the Chief Scientific Officer, CEO, and Development Team, within the scope of a focused globalization strategy, to establish contacts, develop relationships, and raise funds to support global conferences in targeted countries or regions. Typical contacts would include international scientists involved in our conference planning, corporate R&D leaders, international foundation program officers, leaders of government scientific agencies, and international philanthropists.

The position requires a strong commitment to science education and to accelerating life science discoveries that benefit the world. A track record of successful fundraising, particularly at an international level, is required, as is familiarity with international science activities/events and a willingness to travel internationally fairly frequently. Previous experience organizing and supporting international scientific meetings or medical conferences is desirable.

Willingness to relocate to the Keystone Symposia offices in Summit County, Colorado – located approximately 60 miles west of Denver in a recreational paradise – is considered crucial to maintain the interactive teamwork culture of the organization. Interested individuals should email a CV/resume and cover letter to the CEO at aiken@keystonesymposia.org or contact Mary Jo Roal, HR Director, at 970 262 2674.

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POSITIONS OPEN



FACULTY POSITIONS University of Washington

Molecular, Cell and Developmental Biology, Neurobiology and Physiology, Ecology, Evolution & Conservation Biology, Organismal Physiology

As part of a long-term hiring plan, the Department of Biology (website: <http://www.biology.washington.edu>) is conducting a search for outstanding scientists in all areas of biology. To enhance a forward-looking faculty while maintaining traditional excellence, we encourage applications this year from candidates working in organismal physiology, cell and developmental biology, or novel syntheses of these areas. A record of outstanding achievement, a promising research program, and a commitment to teaching are more important than the specific research topic or study organism. Tenure-track appointments at the ASSISTANT or ASSOCIATE PROFESSOR rank are anticipated. Priority will be given to applications received by 15 October 2009 at website: <http://www.biology.washington.edu/fachires/>. Applicants must have earned a doctorate by the date of appointment. All University of Washington faculty engage in teaching, research, and service. UW is an Affirmative Action, Equal Opportunity Employer. We have a culturally diverse faculty and staff and strongly encourage applications from women, minorities, individuals with disabilities, and covered veterans.

TENURE-TRACK FACULTY POSITION in Neuropathology and Complementary and Alternative Medicine

The Department of Pathology, Microbiology and Immunology, School of Medicine, University of South Carolina, Columbia, is undergoing expansion. Applications are invited for a tenure-track ASSISTANT/ASSOCIATE PROFESSOR position in neuropathology/complementary and alternative medicine (CAM). Candidates for Assistant Professor must have a Ph.D. or M.D. or equivalent with postdoctoral research experience. Candidates for Associate Professor must have current extramural funding. Candidates are expected to develop a strong, extramurally funded research program and participate in the teaching mission of the Department. Experience in teaching medical parasitology will be a plus. Opportunities to collaborate with members of the USC Center for CAM exist. Apply with curriculum vitae, statement of research plans, and three letters of recommendation to: Dr. Mitzi Nagarkatti, Chair, Department of Pathology, Microbiology and Immunology, University of South Carolina School of Medicine, Columbia, SC 29208. Or e-mail: neuropath.cam@uscmed.sc.edu. The search will start immediately and continue until the position is filled. USC Columbia is an Equal Opportunity/Affirmative Action Employer and encourages applications from women and minorities.

PHYSIOLOGIST/CELL BIOLOGIST

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Chief, Cardiovascular Division
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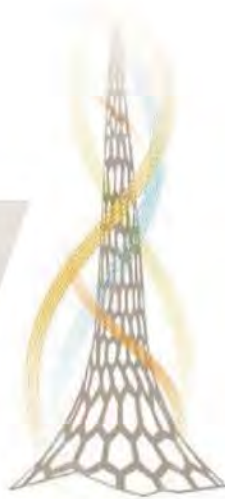
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TENURE-TRACK POSITION in Organismal Physiology College of Charleston

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Applications are invited from suitably qualified scientists wishing to develop their scientific research career as a group leader at the newly established EMBL Australia Partner Laboratory Hub at the Australian Regenerative Medicine Institute at Monash University, Melbourne, Australia. Australia is the first Associate Member of the European Molecular Biology Laboratory (EMBL). EMBL Australia provides Australian researchers access to EMBL through activities such as funded research positions, collaborative ventures and the formation of research institutes.

Group Leader Opportunities at EMBL Australia (2 Positions)

EMBL is an international research organisation offering a highly collaborative, uniquely international culture. It fosters top quality, interdisciplinary research by promoting a vibrant environment consisting of young independent research groups composed of outstanding graduate students and postdoctoral fellows. The scientific programme of EMBL emphasises experimental analysis at multiple levels of biological organisation, from the molecule to the organism, as well as computational biology, bioinformatics and systems biology. In addition to exciting colleagues, the laboratory provides excellent shared facilities for a variety of advanced experimental approaches. High-level expertise is also available in computational biology, diverse aspects of experimental molecular biology as well as physics, biophysics, chemical biology and instrument development.

The EMBL Australia Partner Laboratory Network (PLN) has been established through a hub and spoke framework to enable academic staff in one research group to have access to the complementary facilities and expertise at other institutions. Each partner laboratory node will comprise a minimum of four complementary research groups to ensure a critical disciplinary mass at that site. Current research partners in the network include Monash University, the Universities of Western Australia, Sydney and Queensland and CSIRO. These organisations have specific interest in life sciences research and extensive networks with other universities and research institutes. The complementarity and willingness to work cooperatively are exhibited in the proposed scientific program developed by the EMBL Australia working group after extensive consultation. The hub laboratory and administrative headquarters of the EMBL Australia Partner Laboratory will be at the Australian Regenerative Medicine Institute (ARMI), a state-of-the-art regenerative medicine research facility located at Monash University's Clayton Campus in Melbourne, Australia. The Institute is a joint venture between Monash University and the Government of Victoria.

The successful candidates will each lead a research group for a period of five years at the Australian Regenerative Medicine Institute at Monash University and will participate in the collegial culture of EMBL. The candidates will also participate in the active development of the new Partner Laboratory and a programme of linking activities with the EMBL in Europe.

The appointment will be for a period of five years.

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Benefits:

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- Monash University offers a range of professional development programs, support for research, study and overseas work, generous maternity leave and flexible work arrangements.

Further information about EMBL Australia can be obtained at www.emblaustralia.org

Further information about the position can be obtained from EMBL Australia Executive Director, Silvio Tiziani (silvio.tiziani@armi.monash.edu.au).

To apply, please email a cover letter, CV (in English), three letters of recommendation and a summary of present and future research interests, quoting ref. no. EA/09/001 in the subject line, to: applications@emblaustralia.org

Closing date: 18 October 2009

www.emblaustralia.org

EMBL



Australian Government

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Applications are invited from suitably qualified scientists wishing to develop their research programme as a group leader at EMBL. In accordance with Australia's associate membership of EMBL, funding from NHMRC is available to support one research group located at one of the five EMBL sites in Europe for a maximum period of five years. The position will then be continued for a further four years at an Australian institution. To be eligible for NHMRC support applicants must be working in a field relevant to human health.

Group Leader

5 years in Europe and 4 years in Australia

EMBL Site: The group's location is dependent on the successful candidate's preferences and the proposed research programme. Options available include Heidelberg (Germany) and the EMBL Outstations in Hinxton (UK), Grenoble (France), Hamburg (Germany) and Monterotondo (Italy).

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EMBL is an international research organisation offering a highly collaborative, uniquely international culture. It fosters top quality, interdisciplinary research by promoting a vibrant environment consisting of young independent research groups composed of outstanding graduate students and postdoctoral fellows. The scientific programme of EMBL emphasises experimental analysis at multiple levels of biological organisation, from the molecule to the organism, as well as computational biology, bioinformatics and systems biology. In addition to exciting colleagues, the laboratory provides excellent shared facilities for a variety of advanced experimental approaches. High-level expertise is also available in computational biology, diverse aspects of experimental molecular biology as well as physics, biophysics, chemical biology and instrument development.

The successful candidate will lead a research group for a period of five years at the selected EMBL site in Europe and will participate in the collegial culture of EMBL. Following the term in Europe, the candidate will continue as a group leader at an Australian institution. The successful applicant will need to select and finalise arrangements with an approved Australian institution prior to the commencement of placement in Europe. The candidate will also participate in a programme of linking activities with the Australian institution while in Europe.

EMBL is an inclusive, equal opportunity employer offering attractive conditions and benefits appropriate to an international research organisation.

Further information about EMBL can be obtained at www.embl.org and about the position from:

- EMBL Director General, Iain Mattaj (dg-office@embl.org) or
- NHMRC Director, Research Activity Section, Vaun Peate (vaun.peate@nhmrc.gov.au).

To apply, please email preferably as a single PDF-file: a cover letter, CV and a concise description of research interests & future research plans, quoting ref. no. S/09/070 in the subject line, to application@embl.de. Please also arrange for 3 letters of recommendation to be emailed to references@embl.de.

Closing date: 18 October 2009

Commencing date in Europe: from mid-2010

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THE CHINESE UNIVERSITY OF HONG KONG

Applications are invited for:-

School of Biomedical Sciences, Faculty of Medicine

Associate Professors / Assistant Professors (Non-clinical)

(Ref. 0910/028(665)/2) (Closing date: October 19, 2009)

A new School of Biomedical Sciences has been established within the Faculty of Medicine since June 2009 through re-organization of research and teaching programmes in the former preclinical departments of Anatomy, Biochemistry (Medicine), Pharmacology, and Physiology. The School now invites applications for full-time Associate Professor(s) / Assistant Professor(s) (non-clinical). Individuals who possess expertise in one or more of the following areas are welcome to apply for the posts of Associate/Assistant Professor(s):

1. Organogenesis; 2. Stem cell biology; 3. Regeneration biology; 4. Developmental biology; 5. Reproductive biology

Applicants should have (i) a PhD, MD, or DVM degree or its equivalent in the biological sciences or related disciplines; (ii) experiences in using cutting-edge approaches including but not limited to live cell imaging, genetics, genomics, proteomics, bioinformatics, or transgenic animal models in research; (iii) a good track record of research and publication in international and peer-reviewed journals in one or more related areas; (iv) the ability to establish an independent research programme. The appointee(s) will (a) teach undergraduate and postgraduate courses as well as general education courses; and (b) apply his/her expertise in one of the aforementioned areas so as to complement and strengthen the School's existing research and teaching activities. Appointments will normally be made on contract basis for up to three years initially commencing March 2010, leading to longer-term appointment or substantiation later subject to performance, funding and mutual agreement.

Salary and Fringe Benefits

Salary will be highly competitive, commensurate with qualifications and experience. The University offers a comprehensive fringe benefit package including medical care, plus a contract-end gratuity for appointments of two years or longer and housing benefits for eligible appointees. Further information about the University and the general terms of service for appointments is available at <http://www.cuhk.edu.hk/personnel>. The terms mentioned herein are for reference only and are subject to revision by the University.

Application Procedure

Please send full resume, copies of academic credentials, a publication list and/or abstracts of selected published papers, together with names, addresses and fax numbers/e-mail addresses of three referees to whom the applicants' consent has been given for their providing references (unless otherwise specified), to the Personnel Office, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong (Fax: (852) 2696 1462) by the closing date. The Personal Information Collection Statement will be provided upon request. Please quote the reference number and mark 'Application - Confidential' on cover.



Harvard Medical School Assistant Professor

Single-molecule approaches to studying biomolecular mechanisms

The Department of Biological Chemistry and Molecular Pharmacology (BMCP) at Harvard Medical School seeks to appoint an Assistant Professor whose research concerns the molecular structures, interactions, and mechanisms underlying cell function. We are particularly interested in candidates who use single-molecule approaches and advanced optical methods to probe the structure and function of macromolecular machines.

Interested candidates should submit a CV, a 3 to 5 page statement of research interests, and have 4 letters of recommendation sent to:

Stephen C. Harrison,
Search Committee Chair
c/o Stephanie Biggs
Biological Chemistry and Molecular
Pharmacology
Harvard Medical School
240 Longwood Ave., C-214
Boston, MA 02115

Application deadline is **November 25, 2009.**

*Harvard University is an Equal
Opportunity Employer. Women and
minorities are strongly encouraged to apply.*



TWO FACULTY POSITIONS University of Missouri School of Medicine Department of Nutrition and Exercise Physiology

The Department of Nutrition and Exercise Physiology, University of Missouri School of Medicine invites applications for two tenured or tenure-track positions at any rank with preference given to applicants at the rank of Assistant or Associate Professor. For the first position, we are specifically interested in an investigator who primarily conducts human nutrition, exercise, or metabolism research in the area of obesity and its associated complications (type 2 diabetes, metabolic syndrome, etc). For the second position, we are interested in an investigator with a research program using experimental models for obesity and the metabolic syndrome that is translational. The newly expanded Department of Nutrition and Exercise Physiology now spans three colleges within the University providing a unique opportunity for the department to utilize resources in the Medical School and on the main campus. Our department mission is focused on investigating the obesity epidemic with a collaborative and interdisciplinary approach that spans from pipette to patient to population to policy. Position qualifications include a PhD, MD or a MD/PhD with postdoctoral experience and a basic or clinical research focus in human subjects. Successful applicants will have or develop an outstanding research program and contribute to School of Medicine teaching activities. Involvement in campus-wide research initiatives relative to obesity, cardiovascular biology, exercise, metabolism, cell signaling and nutrition is desirable. Located midway between St. Louis and Kansas City, Columbia is a vibrant university town that is consistently ranked among the top small cities to live in America.

Please send a curriculum vitae, a narrative of research and educational interests, and the names and contact information of three references to:

Frank Booth, Chair, Nutrition and Exercise Physiology Search Committee
Department of Nutrition and Exercise Physiology
School of Medicine/HES/CAFNR
217 Gwynn Hall
University of Missouri-Columbia
Columbia, MO 65211

Or by electronic submission (strongly preferred) to: umchesnsjobs@missouri.edu

Active review of applications will begin **November 1, 2009**, and the search will continue until the position is filled.

The University of Missouri is very interested in promoting a diverse work environment and has programs in place, such as an NSF ADVANCE grant, to promote diversity on campus. The University of Missouri is an Equal Opportunity, Affirmative Action Employer, and complies with the guidelines set forth in the Americans with Disabilities Act of 1990. Visit the University of Missouri-Columbia's website at <http://www.missouri.edu>. Please direct ADA accommodation requests to our coordinator at 573-884-7278 (V/TTY).



UNIVERSITY OF MICHIGAN CENTER FOR STEM CELL BIOLOGY

The University of Michigan invites applications for tenure track **ASSISTANT PROFESSOR** positions. We are seeking outstanding scholars, with Ph.D., M.D. or equivalent degrees and relevant postdoctoral experience, who show exceptional potential to develop an independent research program that will address fundamental issues in any aspect of stem cell biology. Applicants who have already established successful independent research programs will be considered for tenured **ASSOCIATE PROFESSOR** or **PROFESSOR** positions.

Applicants should send a curriculum vitae, copies of up to three reprints, a one- to two-page summary of research plans, and arrange to have three letters of reference sent directly by **October 31, 2009** to: **Stem Cell Search Committee, c/o Rebecca Fritts, Life Sciences Institute, University of Michigan, 210 Washtenaw Avenue, Ann Arbor, Michigan, 48109-2216.**

*The University of Michigan is an Affirmative
Action/Equal Opportunity Employer.*



Singapore
Bioimaging Consortium

RSA
Executive Search

Executive Director

This is an excellent opportunity to lead and develop a well-funded, modern international facility with growing research expertise and capabilities in molecular, cellular and whole animal imaging.

The Singapore Bioimaging Consortium (SBIC) is a member of the Agency for Science, Technology and Research (A*STAR). The Consortium aims to harness local and international imaging expertise into a focused national platform to support multi-disciplinary research activities – spanning the biological, chemical, physical, engineering and clinical sciences – in order to expedite development of new biomedical research discoveries and applications. SBIC will also provide a focal point for interaction with pharmaceutical and biotechnology companies to explore joint research collaborations or business ventures.

SBIC started in 2007 at the Biopolis Research site and has been pioneered by Professor Sir George Radda - former Chief Executive of the UK Medical Research Council and an international authority on imaging. The SBIC currently comprises 70 scientists and support staff, including 7 Principal Investigators, and four technology platforms: Optical Imaging, Image Processing and Management, Small Animal Imaging with Magnetic Resonance, and Development of Chemical/ Biological probes. These technology platforms will be used to support research in areas such as cancer, metabolic disease and regenerative medicine.

Due to Professor Radda's recent appointment as Chairman of A*STAR's Biomedical Research Council (BMRC), we now seek an Executive Director to lead the SBIC.

To discuss your interest in strict confidence, please contact Dr Kevin Young or Laura Thomas at the RSA Group: Kevin.Young@theRSAGroup.com (+44 1707 259333); Laura.Thomas@theRSAGroup.com (+65 6774 4216)

He/she:

- will be responsible for proposing and directing scientific strategies (to be ratified by BMRC) and for the day-to-day management of SBIC
- will manage an interactive institute that engages with other A*STAR organisations, Universities, the biopharmaceutical and food industries
- will be skilled in working at all levels of science management – able to gain the respect of senior and junior staff

You should

- be an MD, MD PhD or PhD with a proven track record of scientific excellence and leadership
- have either direct experience of imaging research and techniques or an appreciation of their role in advancing biomedical science
- possess strategic vision in biologically-driven translational science and well-developed interpersonal, communication and mentoring skills

Metabolic medicine is a central theme of the SBIC's research programmes. Therefore, knowledge of a relevant field of research, such as mitochondrial biology or mechanisms of cell signalling, would be particularly useful.

With the appointment of an Executive Director, Professor Radda will remain as Chairman only.

The terms and conditions on offer are excellent (commensurate with experience) to reflect the importance of this role to A*STAR's future science programmes.



2 Tenure-Track Assistant Professor Positions:

Cellular Biology Evolutionary Developmental Biology (Evo/Devo)

The Department of Biology at the University of Massachusetts Amherst (www.bio.umass.edu/biology) invites applications for two tenure-track assistant professorships, one in the area of Cellular Biology and the other in the area of Evolutionary/Developmental Biology (Evo/Devo). The UMass Biology Department provides an interactive and broad research environment, with faculty research spanning levels of biological organization. Especially strong research clusters focus on the areas of Neural Developmental, Cell Biology, Plant Biology, Functional Morphology, and Evolution. Successful candidates will have a Ph.D., postdoctoral experience, and the potential to develop and maintain an extramurally funded research program. New faculty members will have the opportunity to participate in strong graduate training programs in Molecular and Cellular Biology (www.bio.umass.edu/mcb), Organismal and Evolutionary Biology (www.bio.umass.edu/oeb), Plant Biology (www.bio.umass.edu/plantbio), and Neuroscience and Behavior (www.umass.edu/neuro).

Cell Biology: We seek a broadly trained cell biologist who examines fundamental questions including, but not limited to: cell division and growth, cytoskeleton and molecular motors, membrane trafficking, cell differentiation and nuclear organization. Candidates with expertise in the creative use of microscopy to address cell biological problems and whose interests complement Departmental and University research strengths are particularly encouraged to apply.

Evolutionary Developmental Biology: The candidate should have a strong record of research examining molecular/cellular mechanisms of development that are of fundamental importance for evolutionary biology. We are interested in candidates whose research addresses issues such as the origin and diversification of body plans, the functional divergence of regulatory pathways into novel developmental systems, or the evolution of body structures. Work with model systems, including nematodes, flies, or fish is encouraged, but outstanding applicants who work on other systems will also be considered. Successful candidates should complement and bridge current departmental research strengths in neural development, evolutionary biology, and functional morphology.

Evaluation of applications will begin on October 5, 2009 and continue until the positions are filled. Positions to be filled contingent upon University funding.

Please send application materials to: Cell Biology Search #R36698, or Evo/Devo Search #R36699, Biology Department, Attn: Karen Nelson, 611 North Pleasant Street, University of Massachusetts, Amherst, MA 01003. Application materials should include a curriculum vitae, research plan, teaching statement, plus the names, phone numbers, and email addresses for 3 references. Three letters of recommendation can either be included in the packet or sent electronically to: cellsearch@bio.umass.edu or evodevosearch@bio.umass.edu

The University is part of the 5 College Consortium (www.fivecolleges.edu) in the beautiful Pioneer Valley in Western Massachusetts, just 2 hours from Boston and 3 hours from New York City.

The University of Massachusetts is an Affirmative Action/Equal Opportunity Employer. Women and members of minority groups are encouraged to apply. The Biology Department is aggressive in its efforts to hire candidates who will enhance the diversity and general balance of the faculty and the sciences.

PENNSTATE



Tenure-Track Position in Neurobiology

The Department of Biology at The Pennsylvania State University invites applications for a tenure-track faculty appointment in **Neurobiology** at the Assistant, Associate, or Full Professor rank. Applicants in all areas of neurobiology will be considered with emphasis on molecular, cellular, and developmental neurobiology addressing important questions in synaptic transmission and plasticity, learning and memory, brain development, or neurodegenerative diseases. Candidates should have a strong record of research accomplishment and a commitment to teaching.

Applications, including a cover letter, curriculum vitae, names of at least three references, and a description of current research interests, should be sent as a single PDF file to neuro2@bio.psu.edu. Review of applications will begin **October 15, 2009**.

Penn State is committed to Affirmative Action, Equal Opportunity, and the diversity of its work force.

THE UNIVERSITY of York

DEPARTMENT OF BIOLOGY

Lectureship in Evolutionary Biology Ref: UoY00496

The Department of Biology at the University of York represents a thriving research community of the highest international calibre. York Biology ranks first-equal among UK broad-spectrum biology departments for the percentage of its research judged "world-leading" by the 2008 UK Research Assessment Exercise. York was also top in the UK for citations per research paper published between 2001 and 2005 in the field of Plant and Animal Science (Thomson Scientific UK).

As part of major developments in the department, we wish to appoint a new Lecturer in Evolutionary Biology. We are seeking an outstanding and dynamic scientist with a proven track record of high quality research. You will be expected to develop a research programme of international standing and develop teaching in the same field. Your research will cover any area of evolutionary biology, including adaptation, phylogenetics, population genetics and environmental genomics.

Salary will be within range: £35,469 to £43,622 per annum, depending upon experience. The expected start date is October 2010.

For further information and to apply on-line, please visit our website: <http://www.york.ac.uk/jobs/> Alternatively contact HR Services on 01904 434835 quoting reference number UoY00496.

Closing date: 8 October 2009.

The University of York is committed to diversity and has policies and developmental programmes in place to promote equality of opportunity.

www.york.ac.uk



UNIVERSITY OF
CAMBRIDGE

A world of opportunities

www.cam.ac.uk/jobs/

The Professorship of Statistics in Biomedicine

The Board of Electors to the Professorship of Statistics in Biomedicine invite applications for this Professorship from persons whose work falls within the general field of the Professorship to take up appointment on 1st April 2010 or as soon as possible thereafter.

Further information may be obtained from the Academic Secretary, University Offices, The Old Schools, Cambridge, CB2 1TT, (email ibise@admin.cam.ac.uk), to whom a letter of application should be sent, together with details of current and future research plans, a curriculum vitae, a publications list, and form PD18 with details of two referees, so as to reach him no later than 15 October 2009.

Informal enquiries may be made to Professor John Todd, Acting Head of the Department of Medical Genetics (telephone +44 (0) 1223 762101, e-mail john.todd@cimr.cam.ac.uk) or Professor Patrick Sissons, Regius Professor of Physic (telephone +44 (0)1223 336738, email regius@medschl.cam.ac.uk).

The University is committed to Equality of Opportunity.



FACULTY POSITIONS SCRIPPS INSTITUTION OF OCEANOGRAPHY UNIVERSITY OF CALIFORNIA, SAN DIEGO

The Scripps Institution of Oceanography (SIO) at the University of California in San Diego (<http://scripps.ucsd.edu>) invites faculty applications (tenure track to tenured) to fill one or more positions in one or more of the fields listed below. We seek motivated, broad-thinking scientist-educators to establish vigorous research programs and provide intellectual leadership in their fields while complementing existing expertise at Scripps, other UCSD departments, and nearby institutions. SIO is a world renowned center of marine research with approximately 200 principal investigators leading research programs on all aspects of earth, ocean and atmospheric sciences.

Successful candidates will be expected to teach classes and supervise research at both the graduate and undergraduate levels. The positions require a PhD degree and a competitive record of publication, as well as evidence of the ability to conduct and fund an active research program consistent with the opportunity to have done so at this career level.

Review of applications will begin on **November 1, 2009**, and will continue until positions are filled. Applicants should send a letter and a CV which includes descriptions of their teaching experience, research interests, a list of publications, immigration status, the position(s) for which they are applying and the names of three potential referees, along with their complete institution address, email address, phone and fax numbers to: Chair Search Committee, Department of the Scripps Institution of Oceanography, University of California, San Diego, 9500 Gilman Dr., La Jolla, CA 92093-0208 USA. Applicants should clearly indicate for which position(s) they are applying using the areas of interest as stated below. Questions about submission of applications may be addressed to **Cristy Whitehead** at 858-534-3205, (gradrecruit@sio.ucsd.edu). Salary will depend on the experience of the successful applicant and will be based on the UCSD pay scales.

Applicants are welcome to include in their cover letter a personal statement summarizing their contributions to diversity.

Biology Section: SIO invites applications to fill a faculty position (with preference at the rank of Assistant Professor) in Biochemistry, Genetics or Physiology with a major emphasis on the study of marine organisms, marine symbioses, or marine communities. Research areas of special interest include (but are not restricted to) protein biochemistry, biogeochemistry, chemical ecology, cellular physiology, and biomaterials. The successful candidate will have the opportunity to synergize with ongoing interdisciplinary research and education in natural products, microbiology, genomics and physiology at the Scripps Center for Marine Biotechnology and Biomedicine within the Biology Section.

Ocean Acidification: SIO invites applications at the Assistant, Associate or Full Professor level in the area of Ocean Acidification. Individuals with interests in the impacts of acidification on ocean life and ecology are encouraged to apply. The successful candidate will be interested in developing a multidisciplinary research program and coordinating with colleagues at Scripps and elsewhere, in addition to being committed to engaging students at both the undergraduate and graduate levels.

Marine Population Dynamics: SIO invites applications at the Assistant, Associate, or Full Professor level for a position in Marine Population Dynamics for Fisheries and Protected Species. Research areas of special interest include population dynamics and stock assessment, management strategy evaluation, climate effects, and ecosystem and food web modeling. This key appointment builds upon a long record of accomplishment and collaboration between Scripps Institution of Oceanography and NOAA Fisheries Service. The successful candidate is expected to play a major role in training future practitioners in the science of population assessment and development of enhanced assessment methods that incorporate environmental variability, food web linkages and spatial heterogeneity.

Earth Section: SIO invites applications to fill a faculty position (with preference at the rank of Assistant Professor) in the sciences of the solid Earth. Areas of particular interest include continental margins, seafloor structure and tectonics, sea-level and cryospheric changes, earthquakes and other natural hazards, theoretical and computational methods, and Earth and planetary history. Candidates should have demonstrated research competence, the ability to develop new and innovative directions in research, and an interest in teaching. Interaction and collaboration with existing programs in the Earth Section at Scripps are welcome, as are research areas that would capitalize on our experimental marine and terrestrial seismic, electromagnetic, and geodetic capabilities. Members of the Earth Section do research in geology, geophysics, chemistry, biogeosciences, glaciology, and climate science (for more information see the Annual Report at: http://sio.ucsd.edu/Research/Research_Units/Earth_Science/)

Oceans and Atmosphere Section: SIO invites applications to fill a faculty position (with preference at the rank of Assistant Professor) in Atmospheric Sciences, Physical Oceanography or Marine Engineering. The successful candidate should have the potential to become a scientific leader. Interest in establishing innovative research and education programs is a prerequisite. Interaction and collaboration with the many existing programs in Marine and Atmospheric Sciences at Scripps is encouraged. Specific areas of interest include the development of technology for observing the ocean, collection and analysis of data, ocean-state estimation and modeling, dynamical meteorology, coastal and near-shore processes, and the role of the ocean and atmosphere in past and present climate.

UCSD is an Equal Opportunity Employer with a strong institutional commitment to excellence through diversity.



Faculty Position(s) in Stem Cell Research at the University of Texas at San Antonio

The Department of Biology and the San Antonio Institute for Cellular & Molecular Primatology (SAICMP) at The University of Texas at San Antonio (UTSA) are seeking outstanding candidates for one or more tenured or tenure-track faculty positions in stem cell research (pending budgetary approval). Rank is open. These positions will join a growing stem cell research group focused on aspects of stem cell biology, tissue engineering and regeneration in humans, nonhuman primates and other model organisms including rodents or lower species.

REQUIRED QUALIFICATIONS: The successful applicant will have a Doctoral degree (Ph.D., M.D. or equivalent) in Biology or a related discipline. Applicants at **Assistant Professor** level will require relevant postdoctoral experience and demonstrated potential for excellence in stem cell research. **Preference will be given to candidates with experience working with somatic stem cells, especially neurological or mesenchymal stem cells**, although experience with other types of stem cells will also be considered. An applicant at the **Associate Professor** level will require all of the above plus an established research program with a record of extramural funding. An applicant at the **Full Professor** level will require all of the above plus a distinguished record of sustained funding and productivity as well as leadership in the field of stem cell research.

RESPONSIBILITIES: This position will include a primary appointment in the Department of Biology at UTSA, with the option to become a member of the SAICMP. The successful applicant will be expected to establish and/or maintain a productive, externally funded individual research program, to participate in collaborative research activities with other members of the SAICMP and/or other investigators at UTSA, and to participate in academic and service activities at UTSA based on standard UTSA policies for all faculty members.

APPLICATION: Applicants must submit, by regular mail, fax, or email, a letter of application, a current dated curriculum vitae, copies of 3 recent publications, a statement of research plans, and the names, addresses (both postal and email), and telephone numbers of three references. Applicants should indicate in a cover letter the rank (assistant, associate, or full professor) of the position for which they are applying. The letter should also include summaries of research and teaching interests. Review of completed applications will begin **October 15, 2009**, and will continue until the positions are filled. Address applications to: **Edwin Barca-Rodriguez, Ph.D., Chair, Department of Biology, The University of Texas at San Antonio, 1 UTSA Circle, San Antonio, TX 78249**. Fax applications to **(210) 458-5658** or email applications to **biofacultyad@utsa.edu**. Applicants who are selected for interviews must be able to show proof that they will be eligible and qualified to work in the United States by time of hire.

UTSA is an Affirmative Action/Equal Employment Opportunity Employer. Women, minorities, veterans, and individuals with disabilities are encouraged to apply. We seek candidates committed to our mission of mentorship serving a diverse student body. Competitive salaries and start-up packages are offered.



Neurobiology Faculty Positions

The Department of Biology at The University of Texas at San Antonio (UTSA) is seeking outstanding candidates for a tenure-track Assistant Professor and a tenured full Professor faculty position in Neurobiology (pending budgetary approval) to join a growing and interactive group of neurobiologists (<http://bio.utsa.edu/neurobiology>). UTSA is one of the fastest growing public universities in Texas and is continuing a rapid expansion in Neurobiology. We have recruited 6 new Neurobiology faculty in the past 5 years, and expect to continue expanding our faculty in this area for at least the next 4 years. The Department of Biology currently has 49 faculty members, state-of-the-art facilities, offers B.S. and M.S. degrees, and a Ph.D. with concentrations in either Neurobiology or Cellular and Molecular Biology.

REQUIRED QUALIFICATIONS (Assistant Professor): Applicants must have a Doctoral degree (Ph.D., M.D. or equivalent) in Biology or a related discipline. The successful candidate will be expected to establish an independent, externally funded research program and to teach at both the undergraduate and graduate levels. **PREFERRED QUALIFICATIONS:** Research program with expertise in neural control of movement, central pattern generation, dynamic changes in neuronal structure, structure, function and localization of voltage sensitive ion channels in the central nervous system, and related disciplines.

REQUIRED QUALIFICATIONS (Full Professor): We seek an established scientist who will help to shape the future of Neuroscience at UTSA. Applicants must have a Doctoral degree (Ph.D., M.D. or equivalent) in Biology or a related discipline. The successful applicant will have a well-established neurobiology research program including a record of sustained funding, productivity, and leadership in his/her field.

RESPONSIBILITIES (both positions): The successful applicant will be expected to maintain an active, externally funded research program; lecture, train students in the laboratory, and to participate in other academic activities at UTSA.

APPLICATION: Applicants must submit, by regular mail, fax, or email, a letter of application indicating the position (Assistant or Full Professor), a current dated curriculum vitae, copies of 3 recent publications, a statement of research plans, and the names, addresses (both postal and email), and telephone numbers of three references. Electronic copies of all documents are preferred. Review of completed applications will begin **October 1, 2008**, and will continue until the position is filled. Address applications to: **David B. Jaffe, Ph.D., Neurobiology Search Committee Chair, The University of Texas at San Antonio, One UTSA Circle, San Antonio, TX 78249**. Fax applications to **(210) 458-5658** or email applications to **biofacultyad@utsa.edu**. Applicants who are selected for interviews must be able to show proof that they will be eligible and qualified to work in the United States by time of hire. Competitive salaries and start-up packages are offered.

UTSA is an Affirmative Action/Equal Employment Opportunity Employer. Women, minorities, veterans, and individuals with disabilities are encouraged to apply. We seek candidates committed to our mission of mentorship and serving a diverse student body.



ASSISTANT PROFESSORS OF BIOLOGY UNIVERSITY OF KENTUCKY

The Department of Biology at the University of Kentucky seeks 2 tenure-track **Assistant Professors** interested in **molecular bases of evolution** and/or **molecular approaches to environmental response**. Other areas of modern biological thought will be considered. We are particularly interested in programs that integrate empirical approaches with theoretical, statistical, or computational methods. Model systems for research are open, ranging from microbes to plants and animals, as are levels of biological organization studied, ranging from molecular genetics and epigenetics of cells to genomics of populations. Applicants must have an earned doctorate and have completed postdoctoral training, and previous research by the successful applicants must be published in premier scientific journals. Evidence of an ability to obtain extramural grant support is preferred. Responsibilities for the successful candidates include establishment of an independent research program that is supported by awards from extramural agencies and contribution to the teaching mission of the Biology Department. For more details on the department and the university, visit our website (<http://biology.uky.edu>) or contact **Dr. Vincent Cassone**, Chair, Department of Biology, vincent.cassone@uky.edu or **(859) 257-6766**.

Applicants should send a letter of application, a curriculum vitae, statements on teaching philosophy and experience, and a description of the applicant's research program electronically to biosearch@uky.edu. Applicants should also arrange for three signed letters of recommendation in pdf. format on official letterhead to be sent to the same electronic address. The review of applications will begin **November 1, 2009**.

The University of Kentucky is an Affirmative Action/Equal Opportunity University that values diversity and is located in an increasingly diverse geographical region. It is committed to becoming one of the top public institutions in the country. Women, persons with disabilities, and members of other underrepresented groups are encouraged to apply. The University also supports family-friendly policies.

TECHNICAL UNIVERSITY OF MADRID (UPM)



"ISAAC PERAL" PROGRAMME

THREE INDUSTRY-ACADEMIA BBVA FOUNDATION-UPM CHAIRS

Applications are called for three chairs that will strengthen institutional research initiatives in:

- **Computational Systems Biology**
- **Structural Biology**
- **Nanosensors**

Further details are available at:

http://www2.upm.es/internacional/Researchers/Post_DoctoralandResearchCareerPositions/IsaacPeralProgramme

Contact Point: nacional.investigacion@upm.es

Gross annual remuneration shall be between 80,000 € - 120,000 € depending on experience plus social benefits as for UPM personnel.

Deadline for applications: **30th September 2009**

UPM Research Career Programmes have obtained a COFUND contract (currently under negotiation) from the PEOPLE's Specific Programme of the 7th Framework Programme (European Commission).



ulm university universität
uulm

The **Faculty of Natural Sciences** at the University of Ulm is seeking for three internationally renowned scientists in experimental Biophysics and Bioanalytics, to strengthen and extend the interdisciplinary key activities in Live Sciences:

A Full Professor in Biophysics in the Institute for Biophysics

(W3 position including head of Institute, following Prof. Dr. G. Ulrich Nienhaus)

Research topics include, but are not limited to, protein dynamics and single-molecule spectroscopy, interaction studies of mechanical stimuli and function of proteins, biological transport processes and signalling.

In the **Institute for Experimental Physics** we look for a

W3-Professor for Bionanomechanics

Topics include mechanics of cells, cell structures and single biomolecules. Methods employing AFMs, optical tweezers, or micro-fluidic setups for medically relevant cells and molecules should be included.

In the **Institute for Analytical and Bioanalytical Chemistry** we search a

W3-Professor for Analytical Chemistry

(following Prof. Dr. Thomas Welsch)

Possible topics include micro-fluidics, lab-on-a-chip or miniaturized separation technologies.

We expect interdisciplinary exchange and interactions within the faculty of natural sciences as well as within the established key activities in biomaterials, nano-medicine or in the field of adult stem cells, which are embedded in the cross sectoral subject of imaging at the University of Ulm.

The applicant in Analytical Chemistry is expected to teach this subject in undergraduate and graduate level courses for Chemists, Biochemists, Biologists, in the master program advanced materials, and for students of the faculty of Medicine. The applicants for Biophysics are expected to teach experimental physics for physicists and majors of other disciplines. Experience in interdisciplinary studies is desired; likewise, active participation in academic responsibilities, administrative tasks and initiatives is expected.

Conditions for appointment are a completed course of studies at a university, pedagogical aptitude, doctorate and additional academic achievements (§ 47 LHG).

The University of Ulm is committed to increase the share of women in research and teaching positions and therefore explicitly encourages female candidates to apply.

Applications should include curriculum vitae, employment certificates, a summary of teaching and research plans, a list of publications with up to three reprints, a short description of current research activities, and a scientific concept. Applications should be sent to the Dean of the Faculty of Natural Sciences, Albert-Einstein-Allee 11, D-89081 Ulm, **by November 13, 2009**. Please indicate on the envelope the **index number 64**.

Physically disabled applicants receive favourable consideration when equally qualified.



One focus: join our shared commitment to improve the lives of cancer patients everywhere.

Now the innovative science of a leading American biopharmaceutical company joins the global assets of Takeda, Japan's largest pharmaceutical company, for a worldwide commitment to oncology.

Millennium: The Takeda Oncology Company is developing an extensive pipeline — among the top in oncology worldwide — with more than 13 compounds in development for a broad range of solid and hematological cancers.

Come to where lifesaving science meets lifechanging opportunities. At Millennium, you'll help develop breakthrough treatments that can make a difference in patients' lives. All in a dynamic, collaborative environment where you can be yourself — and do your best science. To learn more or apply, visit us at millennium.com.

Millennium has opportunities in the following areas:

- | | |
|---|--|
| <ul style="list-style-type: none"> ■ Analytical Development ■ Biostatistics & Medical Writing ■ Clinical Data Operations ■ Clinical Operations ■ Clinical Pharmacology ■ Clinical Research – Oncology ■ Commercial & Business Systems ■ Global Marketing ■ Government Relations – Public Policy ■ Imaging Sciences ■ Lead Discovery ■ Legal – Business Law ■ Medical Directors | <ul style="list-style-type: none"> ■ Medicinal Chemistry ■ Medical Science Liaisons ■ Molecular Medicine ■ New Product Marketing ■ Pharmacovigilance ■ Postdoctoral Program – Protein Homeostasis ■ Reimbursement & National Accounts ■ Regulatory Affairs – CMC ■ Regulatory Affairs – Therapeutics ■ Regulatory Operations |
|---|--|

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Assistant Professor of Integrative Biology/Animal Ecologist

The Department of Biology at The University of Texas at San Antonio (UTSA) is seeking outstanding candidates for a tenure-track assistant professor faculty position in Integrative Biology (pending budgetary approval) to join a growing group of integrative biologists (<http://www.bio.utsa.edu/facultyrec.html>). Applicants for the Integrative Biology position should have a specialty in animal ecology with particular interest in global change pertaining to biological phenomena. We seek an assistant professor who would help to shape the future of Integrative Biology at UTSA. The Department of Biology currently has approximately 50 faculty members with general interest in Cellular and Molecular Biology, Integrative Biology, Microbiology and Immunology and Neurobiology, and offers B.S. and M.S. degrees, and a Ph.D. with concentrations in Neurobiology, and Cellular and Molecular Biology. We expect to expand the number of Ph.D. concentrations to include integrative biology in the near future.

REQUIRED QUALIFICATIONS: Applicants must have a Doctoral degree (Ph.D. or equivalent) in biology, integrative biology, animal ecology or a related discipline. Post- Doctoral experience is preferred.

RESPONSIBILITIES: The successful applicant will be expected to develop and maintain an active, externally funded research program, lecture, train students in the field and laboratory, and to participate in other academic activities at UTSA.

APPLICATION: Applicants must submit, by regular mail, fax, or email, a letter of application, a current dated CV, copies of recent publications, a statement of research plans and teaching interests and philosophy, and the names, addresses, and telephone numbers of three references. Review of completed applications will begin **November 1, 2009**, and will continue until the position is filled. Address applications to: **Integrative Biology Search Committee, The University of Texas at San Antonio, 1 UTSA Circle, San Antonio, TX 78249.** Fax applications to (210) 458-5658 or email applications to biofacultyad@utsa.edu. Applicants who are selected for interviews must be able to show proof that they will be eligible and qualified to work in the United States by time of hire. Competitive salaries and start-up packages are offered.

UTSA is an Affirmative Action/Equal Employment Opportunity Employer. Women, minorities, veterans, and individuals with disabilities are encouraged to apply. We seek candidates committed to our mission of mentorship and serving a diverse student body.



THE UNIVERSITY OF TEXAS AT SAN ANTONIO LIFE SCIENCES EDUCATION FACULTY POSITION

The Department of Biology at The University of Texas at San Antonio invites applications for a tenure-track/tenured faculty position in **Life Sciences Education**, preferably at the **Associate/Full Professor** level starting Fall of 2010 pending budget approval. Successful applicants for this position should have experience in teaching and research in Life Sciences education, preferably in a large classroom environment. The applicant will be expected to carry out a successful research program in undergraduate science education. Responsibilities may include teaching and curriculum development and course redesign of lecture and laboratory curricula for introductory and other courses central to the biology degree, outreach activities in the educational community and development of a science teacher training program. Required qualifications include a doctoral degree in Biology or Life Sciences education or a related field and academic achievement in Life Science education. The Department offers the Ph.D., M.S., B.S., and B.A. degrees in biology. Screening of applications will begin immediately and continue until the position is filled.

Applicants must submit an original signed letter of application stating rank applied for, current dated vita, description of experience in Life Sciences education and the names and addresses of three professional references. These materials should be sent to: **Chair, Educator Search Committee, Department of Biology, The University of Texas at San Antonio, One UTSA Circle, San Antonio, Texas 78249-0662** or email to biofacultyad@utsa.edu. Applicants who are selected for interviews must be able to show proof that they will be eligible and qualified to work in the United States by time of hire.

The University of Texas at San Antonio is an Affirmative Action/Equal Opportunity Employer. Women, minorities, veterans, and individuals with disabilities are encouraged to apply.



McGOVERN INSTITUTE

FOR BRAIN RESEARCH AT MIT

The McGovern Institute for Brain Research at MIT is seeking one faculty member at the **Assistant Professor** level. The McGovern Institute's general focus is in systems neuroscience with an emphasis on the neural basis of perception, cognition, and action. We are seeking a candidate with a research focus in any of these three areas, using either human subjects or animal models. We would regard it as a plus if the candidate's work bridges levels using a variety of tools and/or the candidate were interested in translating basic research findings into new ideas for studying the pathophysiology or treatment of brain disorders.

The mission of the McGovern Institute is to understand the relationship of neuronal processes, circuits and computations to behavior, ultimately providing benefits to human health and welfare. Research in the McGovern Institute is expected to help people with brain disorders ranging from sensory system impairments to movement disorders and emotional and cognitive disorders. McGovern Institute scientists have many opportunities for collaboration in a diverse and cutting-edge environment. In the fall of 2005, the Institute moved to occupy a new building, which includes a brain imaging center for human subjects and animals. McGovern Institute members are appointed through an MIT department and will have teaching responsibilities for their home department.

Applicants should submit a curriculum vitae, a summary of current and proposed research programs, a publication list, and should arrange for three letters of recommendation to be sent electronically via Academic Jobs Online (<https://academicjobsonline.org/ajol/>). Please indicate which research model, animal or human, you are using in your cover letter. Consideration of applications will begin on **November 1, 2009** and will continue until the position is filled. For more information on the McGovern Institute please visit our website at <http://web.mit.edu/mcgovern>.

MIT is an Affirmative Action/Equal Opportunity Employer. Qualified women and minority candidates are especially encouraged to apply.



Editor, Trends Journals

Cell Press seeks to appoint Editors for its prestigious Trends titles, in its Cambridge, Massachusetts office, with possible opportunities for the following Trends Journals: Biotechnology, Cell Biology, Cognitive Sciences, Genetics, Immunology, Microbiology, Molecular Medicine, Neurosciences, Parasitology, and Pharmacological Sciences.

As the Editor of one of these leading international reviews journals, you will be responsible for the strategic development and management of the content and editorial direction of the journal. You will be acquiring, managing and developing the very best editorial content, making use of a network of contacts in academia, as well as exploiting information gathered at international conferences, to ensure the title maintains its market-leading position. You will collaborate with your Cell Press colleagues to maximize quality and efficiency of content commissioning and participate in exciting new non-journal based initiatives. The Editor will be trained and will work in the context of this highly dynamic and collaborative publishing group which includes the 14 Trends titles and 12 Cell Press titles.

This is an exciting and challenging role and you will need a PhD in a relevant discipline. Good interpersonal skills are essential because the role involves networking in the wider scientific community as well as collaborations with other parts of the business.

For this position, previous publishing experience is not necessary. This is an ideal opportunity to stay close to the cutting edge of scientific developments in the field while developing a new career in an exciting publishing environment. To apply, please submit a CV and cover letter via the Careers section of Elsevier's website, www.elsevier.com, indicating the Trends journal Editor position to which you are applying, and describing your qualifications, research interests, and reasons for pursuing a career in publishing. No phone inquiries, please. Applications will be considered on an ongoing basis through **October 9, 2009**.

Cell Press is an Equal Opportunity/Affirmative Action Employer. M/F/D/V.



FACULTY POSITIONS

Sealy Center for Vaccine Development, Center for Biodefense and Emerging Infectious Diseases, and Department of Pathology, University of Texas Medical Branch at Galveston



Assistant, Associate or Full professor level, tenure track positions are available for persons with MD, PhD, and/or DVM degrees. UTMB has a very rich environment for infectious diseases research. In addition to the Sealy Center for Vaccine Development (www.utmb.edu/scvd), it is home to the NIAID-supported Western Regional Center of Excellence in Biodefense and Emerging Infectious Diseases (www.rcebidefense.org/rce6/rce6pub.htm), the Galveston National Laboratory, the Center for Biodefense and Emerging Infectious Diseases (www.utmb.edu/CBEID/links.shtml), the Center for Hepatitis Research, the Institute for Human Infections and Immunity, the Institute for Translational Science, and the Sealy Center for Structural Biology and Molecular Biophysics. This wealth of expertise and state-of-the-art high containment BSL-3 and BSL-4 and core facilities offer outstanding opportunities for collaboration and multidisciplinary research with over 150 scientists focusing on infectious disease/immunology research.

The city of Galveston, a popular tourist destination that includes beaches, museums, historical sights, 2 cruise lines, and excellent restaurants, is 45 minutes away from Houston, the nation's fourth largest city. UTMB is home to the oldest medical school in the state and has infectious diseases research expertise and facilities that are rivaled by few, if any, universities in the country.

VACCINOLOGIST: The Sealy Center for Vaccine Development seeks individuals with proven abilities in vaccine-related research who have demonstrated academic scholarship in the form of publications in major peer-reviewed journals, a record of continued extramural research funding or the potential to establish a funded program, and a willingness to work in a highly collaborative and interdisciplinary environment. Particular attention will be given to those interested in the following areas of vaccine development: BSL-4 virology, adjuvants, vaccine delivery systems/platform technologies, and/or vaccine safety.

Interested individuals should send a C.V. and an outline of their research interests to: **Vaccinologist Search Committee C/O Sandra Rivas, Sealy Center for Vaccine Development** (smrivas@utmb.edu). For additional information, contact **Dr. Alan Barrett**, Director, Sealy Center for Vaccine Development (abarrett@utmb.edu; phone 409-772-6662).

VIROLOGIST: A virologist with proven abilities in research relating to zoonotic and emerging viruses such as arboviruses, rodent-borne or hemorrhagic fever viruses is sought. Applicants working at high containment (BSL-3 or BSL-4) will receive special consideration, as well as those studying virus-vector or virus-host interactions. Applicants should demonstrate the ability or potential to compete for research funding and have a strong publication record.

Interested candidates should send a C.V., outline of research interests and names of four references electronically to dwalker@utmb.edu, or by mail to: **Virology Search Committee C/O Sherrill Hebert, UTMB Department of Pathology, 301 University Blvd, Galveston, TX, 77555-0609**. For additional information, contact **Dr. Scott Weaver**, Vice Chair for Research, Department of Pathology (sweaver@utmb.edu; phone 409-747-0758).

*The University of Texas Medical Branch at Galveston is an Equal Opportunity, Affirmative Action Institution, which proudly values diversity.
Candidates of all backgrounds, including persons with disabilities, are encouraged to apply.*



國家衛生研究院
National Health Research Institutes

Principal Investigator Positions Division of Infectious Diseases National Health Research Institutes (NHRI) Taiwan

The Division of Infectious Diseases of National Health Research Institutes, Taiwan aims at studying important infectious diseases and their molecular mechanisms, treatment and preventions. Positions open at the rank of Assistant, Associate or full Investigator to participate in studies on antimicrobial resistance of bacterial/fungal pathogens and the pathogenesis of bacterial, fungal and viral infections. Candidates should have a Ph.D. and/or M.D., as well as extensive post doctoral experience. Physicians with training in infectious diseases and interested in research are specially welcome.

Applicants should send curriculum vitae, description of research accomplishments, future research activities, and three reference letters to:

Ms Nicole Wang (880827@nhri.org.tw)
Division of Infectious Diseases
National Health Research Institutes
35 Keyan Road
Zhunan Town
Miaoli County 35053
Taiwan ROC
Fax: 886-37-586457

Application deadline: November 30, 2009.



**MEDICAL
COLLEGE
OF WISCONSIN**

Tenure Track Faculty Position in Stem Cell Biology and Regenerative Medicine

Medical College of Wisconsin
Department of Cell Biology, Neurobiology
and Anatomy (<http://www.mcw.edu/cellbio.htm>)/Regenerative Medicine
Program (<http://www.mcw.edu/regenerativemedicine.htm>).

A tenure track faculty position at the Assistant or Associate Professor level is available for a developmental/cell biologist that uses cellular and/or molecular-genetic approaches to address fundamental aspects of cell differentiation. Candidates interested in the study of regenerative medicine using stem cells are particularly encouraged to apply. Competitive salary, laboratory space and start-up funds are available. Candidates at the Associate Professor level are expected to bring a vigorous research program with significant extramural funding. Current research strengths in the department include developmental biology of the liver, gastrointestinal, cardiovascular, and ocular systems. A Ph.D. or MD/Ph.D. degree (or equivalent), plus additional postdoctoral experience are essential. Interested individuals should send a resume, research plans, and the names of three references to:

Dr. Stephen A. Duncan
Chairman, Search Committee
Regenerative Medicine Program
Department of Cell Biology, Neurobiology and Anatomy
Medical College of Wisconsin
8701 Watertown Plank Rd
Milwaukee, Wisconsin 53226-0509

The Medical College of Wisconsin in Milwaukee, Wisconsin is a private freestanding institution established in 1967 that enrolls approximately 800 medical students, 440 graduate students, and 200 scientists engaged in post-doctoral research. MCW is one of the fastest growing medical colleges in the U.S. and ranks in the top third of all US schools receiving NIH support. In FY 2008-09, faculty received approximately \$146 million in external support for research, teaching, training and related purposes.

AA/EOE



CHEMICAL PHYSICS SEARCH

California Institute of Technology invites applications for a tenure-track faculty position in the Division of Chemistry and Chemical Engineering in the area of chemical physics and related fields. Candidates with strong commitments to research and teaching excellence are encouraged to apply. We expect to make the appointment at the **ASSISTANT PROFESSOR** level, but consideration will be given to exceptionally well-qualified applicants at the **ASSOCIATE** and **FULL PROFESSOR** levels. Appointment will be contingent upon completion of all requirements for a Ph.D. in chemistry or in a related field. Submit curriculum vitae, publication list, a description of proposed research, and three letters of recommendation to: **Chair of the Chemical Physics Search Committee, M/C 127-72, California Institute of Technology, Pasadena, CA 91125**. Applications should be received by November 1, 2009. *The California Institute of Technology is an Equal Opportunity/Affirmative Action Employer. Women, minorities, veterans, and disabled persons are encouraged to apply.*



CHEMICAL ENGINEERING SEARCH

California Institute of Technology invites applications for a tenure-track faculty position in the Division of Chemistry and Chemical Engineering in the area of chemical engineering. Candidates with strong commitments to research and teaching excellence are encouraged to apply. We expect to make the appointment at the **ASSISTANT PROFESSOR** level, but consideration will be given to exceptionally well-qualified applicants at the **ASSOCIATE** and **FULL PROFESSOR** levels. Appointment will be contingent upon completion of all requirements for a Ph.D. in chemical engineering or in a related field. Submit curriculum vitae, publication list, a description of proposed research, and three letters of recommendation to: **Chair of the Chemical Engineering Search Committee, M/C 210-41, California Institute of Technology, Pasadena, CA 91125**. Applications should be received by November 1, 2009. *The California Institute of Technology is an Equal Opportunity/Affirmative Action Employer. Women, minorities, veterans, and disabled persons are encouraged to apply.*



ORGANIC CHEMISTRY SEARCH

California Institute of Technology invites applications for a tenure-track faculty position in organic chemistry in the Division of Chemistry and Chemical Engineering. Appointment will be contingent upon completion of all requirements for a Ph.D. in chemistry or a closely related field. Outstanding candidates who have strong commitments to research and teaching are encouraged to apply. We expect to make the appointment at the **ASSISTANT PROFESSOR** level, but consideration will be given to exceptionally well-qualified applicants at the **ASSOCIATE** and **FULL PROFESSOR** levels. Submit by November 1, 2009, your curriculum vitae, a publication list, a concise description of proposed research, and three letters of recommendation to: **Chair, Organic Faculty Search Committee, MC 164-30, California Institute of Technology, Pasadena, CA 91125**. *The California Institute of Technology is an Equal Opportunity/Affirmative Action Employer. Women, minorities, veterans, and disabled persons are encouraged to apply.*



ENDOWED CHAIR IN DRUG DISCOVERY

The Department of Chemistry and Department of Medicinal Chemistry and Molecular Pharmacology at Purdue University are pleased to announce the availability of an endowed Chair faculty position in drug discovery and development.

We seek an exceptional scientist with an outstanding track record of creativity in any area related to the science of drug discovery. Candidates seeking to advance their own discoveries through early stages of clinical trials are particularly encouraged to apply. Purdue University offers a thriving interdisciplinary research and education environment, including unique capabilities within Discovery Park, with excellent faculty, and exceptional support services associated with drug discovery and preclinical testing. More details about the departments involved in this search at Purdue can be found at websites: <http://www.chem.purdue.edu> or <http://www.mcmp.purdue.edu>. Applicants should send curriculum vitae, a summary of planned research, and the names of three references to: **Prof. Paul B. Shepson, Department Head, Department of Chemistry, Purdue University, 560 Oval Drive, West Lafayette, IN 47907-2084**. Review of applicants will begin in October 2009 and continue until the position is filled.

Purdue University is an Equal Opportunity/Equal Access/Affirmative Action Employer fully committed to achieving a diverse work force.

TENURE-TRACK FACULTY POSITION in Health Sciences Purdue University School of Health Sciences

The College of Pharmacy, Nursing and Health Sciences is a triumvirate of Schools at Purdue University concentrating on human health. The School of Health Sciences continues expansion of its research programs in environmental/occupational toxicology and radiological health sciences (health physics and medical physics). We invite applications for a tenure-track position at **ASSISTANT** or **ASSOCIATE PROFESSOR** level. The successful candidate is expected to develop and maintain an extramurally funded research program in environmental, occupational, toxicological, or radiological health sciences. Applicants with expertise in molecular, cellular, animal model, imaging, and/or computational experimental approaches related to understanding the mechanisms of external agents on human health are encouraged to apply. Candidates must have a Ph.D., M.D., or equivalent degree and at least two years of relevant postdoctoral research experience. The position is competitive with regard to salary, startup funds, and laboratory space. Please electronically submit curriculum vitae, a brief statement of current and future research interests, and contact information for three references to: **Dr. Gary Carlson, Professor and Chair of the Search Committee, e-mail: gcarlson@purdue.edu**. Applicants are encouraged to apply by December 1, 2009, for full consideration.

Purdue University is an Equal Opportunity/Equal Access/Affirmative Action Employer fully committed to achieving a diverse work force.

POSTDOCTORAL POSITIONS Available at Sloan-Kettering Institute

Seeking research scientists with postdoctoral experience to join a laboratory developing therapeutic approaches to target the molecular events underlying leukemic hematopoiesis. Applicants must have interest and expertise in studying hematopoietic stem cell biology or myeloid leukemogenesis using mouse models and/or in vitro culture techniques. Send a description of your research interests, curriculum vitae, and the names and telephone numbers of three references to: **Dr. Stephen D. Nimer, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 575, New York, NY 10065**.



The Department of Chemistry and Biochemistry at the University of Texas at Austin invites applications for tenure-track positions at the **ASSISTANT PROFESSOR** level. All areas of chemistry and biochemistry will be considered, but interdisciplinary fields are especially encouraged. For additional information and applicant instructions, visit website: <http://www.cm.utexas.edu>. Applications received after October 16, 2009, may not receive full consideration. *The University of Texas is an Equal Opportunity and Affirmative Action Employer.*

VERTEBRATE BIOLOGY FACULTY POSITION

The Department of Biology at Clark University, Worcester, Massachusetts (website: <http://www.clarku.edu/departments/biology/>), invites applications for a tenure-track appointment at the rank of **ASSISTANT PROFESSOR** to begin fall 2010. The successful candidate will be expected to develop an externally funded research program in any area of vertebrate biology involving Ph.D. and undergraduate students. The candidate will teach a comparative and/or human anatomy course(s) as well as courses in the area of expertise. Electronic copies of curriculum vitae, research and teaching interests, three publications, and three letters of reference should be received by the Search Committee prior to October 30, 2009, for full consideration at e-mail: vert@clarku.edu. Please see website: <http://www.clarku.edu/biologysearch> for full position description. Inquiries should be directed to e-mail: dhibbett@clarku.edu. *Affirmative Action/Equal Opportunity Employer. Minorities and women are strongly encouraged to apply.*

BIOLOGY

The College of Wooster Department of Biology invites applications for a tenure-track **ASSISTANT PROFESSOR** position beginning August 2010, to teach courses in invertebrate zoology, animal behavior, and introductory biology; to direct undergraduate research in the College's required Independent Study Program; and to teach occasionally in the College's interdisciplinary First-Year Seminar program. Ability to teach introductory biostatistics is a plus. Applicants should have a Ph.D.; postdoctoral research and/or teaching experience preferred. Send curriculum vitae, statements on research and teaching philosophy, official transcripts, and three letters of recommendation by October 23, 2009, to: **Dr. M. D. Loveless, Department of Biology, The College of Wooster, 931 College Mall, Wooster, OH 44691**. *Wooster seeks to ensure diversity by its policy of employing persons without regard to age, sex, color, race, creed, religion, national origin, disability, veteran status, sexual orientation, or political affiliation. The College of Wooster is an Equal Opportunity/Affirmative Action Employer.*

ENTOMOLOGIST

Tenure-track **ASSISTANT PROFESSOR** in biology with specialty in entomology beginning 1 September 2010. Ph.D. required; postdoctoral and teaching experience desirable. Responsibilities: teach entomology, biology of animals, and introductory biology; develop research program in entomology; pursue extramural funding; supervise M.S. theses; supervise maintenance of extensive insect collection; advise students. Send letter of application, brief statements of teaching philosophy and research interests, curriculum vitae, reprints, three current letters of recommendation, and transcripts (official or photocopy) to: **Chair, Department of Biology and Microbiology, University of Wisconsin Oshkosh, Oshkosh, WI 54901** by November 6, 2009. For additional information, see website: <http://www.uwosh.edu/departments/biology/>. *Employment requires criminal background check. Affirmative Action/Equal Opportunity Employer.*



UNIVERSITY OF
LIVERPOOL

Department of Chemistry

Postdoctoral Researchers

£30,594 - £32,458 pa (under review)

Thirteen positions are available under the Themes of porous materials, oxides and nanomaterials. The positions require skills in synthesis, characterisation and measurement of new materials, and unified by the ability to work with initiative and independence in a multidisciplinary team at the highest scientific level, demonstrated by publications. You should have a PhD in Chemistry, Materials Science or Physics with an excellent publication record. Three positions are for Theme Leaders, requiring organisational and leadership skills, and ten to work in and across the Themes. The posts, funded by the EPSRC are available for 3 years.

Job Ref: R-570608/SCI Closing Date: 9 October 2009

For full details, or to request an application pack, visit www.liv.ac.uk/working/job_vacancies/ or e-mail jobs@liv.ac.uk

Tel 0151 794 2210 (24 hr answerphone)

Please quote Job Ref in all enquiries.

COMMITTED TO DIVERSITY AND EQUALITY OF OPPORTUNITY



Center for Learning and Memory Institute for Neuroscience The University of Texas at Austin

The Center for Learning and Memory at the University of Texas at Austin invites applications for a number of tenure track faculty positions at the **assistant professor** level. While the field of research is open, we are particularly interested in candidates using genetic and molecular approaches to investigate plasticity and learning and in candidates using systems levels of analyses of learning and memory in behaving animals. This recruitment effort is partially supported by a P30 Faculty Recruitment Grant from the National Institute of Mental Health and as such the research areas of successful candidates will be expected to fit within the overall basic science mission of the NIMH. Successful candidates will join an expanding and vibrant neuroscience environment within the Center for Learning and Memory and the Institute for Neuroscience and will be expected to develop and maintain an active research program while having minimal teaching responsibilities. Academic appointments will be made in the appropriate academic unit within the College of Natural Sciences, College of Liberal Arts, School of Pharmacy, or School of Engineering. The positions will include competitive salary and start-up packages and have laboratories within Center for Learning and Memory in the Neural and Molecular Sciences Building located in the heart of the beautiful UT campus.

Austin is located in the Texas hill country and is widely recognized as one of America's most beautiful and livable cities (see: www.austintexas.org/home/). Please send curriculum vitae, summary of research interests, and names of five references to:

Dr. Daniel Johnston, Director
Center for Learning and Memory
The University of Texas at Austin
1 University Station, C7000
Austin, TX 78712-0805

Homepage: <http://clm.utexas.edu/>

The University of Texas at Austin is an Equal Opportunity Employer. Qualified women and minorities are encouraged to apply; a background check will be conducted on applicants selected.

THE UNIVERSITY OF HONG KONG



Founded in 1911, The University of Hong Kong is committed to the highest international standards of excellence in teaching and research, and has been at the international forefront of academic scholarship for many years. Of a number of recent indicators of the University's performance, one is its ranking at 26 among the top 200 universities in the world by the UK's *Times Higher Education*. The University has a comprehensive range of study programmes and research disciplines, with 20,000 undergraduate and postgraduate students from 50 countries, and a complement of 1,200 academic members of staff, many of whom are internationally renowned.

Post-doctoral Fellowships and Research Assistant Professorships

Applications are invited for a number of positions as Post-doctoral Fellow (PDF) (Ref: RF-2009/2010-136) and Research Assistant Professor (RAP) (Ref: RF-2009/2010-137), at the University of Hong Kong, on or before July 31, 2010. Appointments will be made for a period of 2 to 3 years.

PDF and RAP posts are created specifically to bring new impetus and vigour to the University's research enterprise. Positions are available from time to time to meet the strategic research needs identified by the University. Positions are available in the following Departments:

- Real Estate and Construction
- School of Humanities
- School of Modern Languages and Cultures
- Faculty of Education
- Computer Science
- Electrical and Electronic Engineering
- AIDS Institute
- Centre for Cancer Research
- Research Centre of Heart, Brain, Hormone and Healthy Aging
- Research Centre of Infection and Immunology
- Medicine
- Microbiology
- Pathology
- Centre for Reproduction, Development and Growth
- School of Biological Sciences
- Chemistry
- The Swire Institute of Marine Science

Post-doctoral Fellows

PDFs are expected to devote full-time to research. Applicants should be doctoral degree holders having undertaken original research that has contributed to the body of knowledge. A highly competitive salary commensurate with qualifications and experience will be offered. Annual leave and medical benefits will also be available.

Research Assistant Professors

The main focus of an RAP's duty is research. RAPs can however be assigned some teaching duties, up to 50% of the normal teaching load. Applicants should be research active and have a proven publication record. A highly competitive salary commensurate with qualifications and experience will be offered, with a contract-end gratuity and University contribution to a retirement benefits scheme (totalling up to 15% of basic salary). Annual leave, and medical/dental benefits will also be offered.

Procedures

Prospective applicants are invited to visit the following webpage <<http://www.hku.hk/apptunit/>> to view the full list of the research areas and their home Faculties/Departments/Schools/Centres for which PDF/RAP positions are currently available. Before preparing an application they should contact the Head of the appropriate academic unit to ascertain that their research expertise matches the research area for which a vacant PDF/RAP post is available.

Applicants must submit a completed University application form, which should clearly state **which position they are applying for**; and in which **academic discipline**. They should also provide further information such as details of their research experience, publications, research proposals, etc.

Further particulars and application forms (152/708) can be obtained at <http://www.hku.hk/apptunit/>; or from the Appointments Unit (Senior), Human Resource Section, Registry, The University of Hong Kong, Hong Kong (fax: (852) 2540 6735 or 2559 2058; e-mail: senrappt@hku.hk). **Closes October 16, 2009.** Candidates who are not contacted within 3 months of the closing date may consider their applications unsuccessful.

The University is an equal opportunity employer and is committed to a No-Smoking Policy



COMPUTATIONAL NEUROSCIENCE The Neurosciences Institute, La Jolla

The Neurosciences Institute seeks **POSTDOCTORAL RESEARCHERS** in computational neuroscience to work with a team to create large-scale spiking models of the mammalian nervous system. In order to understand how neuroanatomy and network dynamics give rise to cognitive functions, the team will use these models to control robotic devices whose behavior changes based on their experience in the world.

Preferred candidates will have a background in neuroscience, previous modeling experience, strong programming skills, and experience with parallel computation.

The Neurosciences Institute provides opportunities for and encourages interactions among researchers in various disciplines in order to elucidate fundamental principles of brain function.

Candidates should send curriculum vitae, including the names of three references, to: **Dr. W. Einar Gall, Research Director, The Neurosciences Institute, 10640 John Jay Hopkins Drive, San Diego, CA 92121. Or e-mail: jobs6@nsi.edu.**

The Neurosciences Institute is an Equal Opportunity Employer.

POSTDOCTORAL FELLOW in Synthetic Chemistry, Peptide Synthesis, and/or Molecular Biology

The Wyss Institute for Biologically Inspired Engineering ([website: http://www.wyss.harvard.edu](http://www.wyss.harvard.edu)) seeks applicants for the position of Postdoctoral Fellow to be a part of a dynamic new research group. The research program is highly interdisciplinary and focused at the interface of chemistry, biology, and engineering. Projects will involve the development of self-assembling systems from protein and peptide building blocks and will be targeted toward specific applications in tissue engineering, drug delivery, and medical imaging.

Applicants should have a Ph.D. with a strong background in synthetic chemistry, peptide synthesis, and/or molecular biology. Experience with nanoscale characterization techniques (atomic force microscopy, transmission electron microscopy, light scattering, and so on) or directed evolution of proteins is preferred. Applicants should be interested in the basic science of self-assembly and biomimicry and its application to medical science. Successful candidates will be eager to lead by example in the laboratory, mentor graduate and undergraduate students, manage research projects, and possess excellent communication skills.

Interested applicants should send a single document PDF containing curriculum vitae, cover letter describing research interests and goals, a full list of publications, copies of up to three relevant scientific papers, and names and contact information for at least three letters of recommendation, who might be contacted as references. Applications should be sent to **e-mail: faculty_postdocs@wyss.harvard.edu.**

Harvard University is an Equal Opportunity/Affirmative Action Employer and applications from women and minority candidates are strongly encouraged.



POSTDOCTORAL/RESEARCH ASSOCIATE POSITIONS are available in the area of mechanism-based cancer prevention using plant-derived compounds and molecular mechanism of carcinogenesis in the laboratory of **Xianglin Shi, University of Kentucky.** Send curriculum vitae to **e-mail: xianglin.shi@uky.edu.**



POSTDOCTORAL RESEARCH POSITIONS

available to study the molecular mechanisms, regulation, and functions of autophagy, including its roles in cell death regulation, cancer biology, and infectious diseases. Ph.D. and/or M.D. required. Candidates should have a strong foundation in molecular biology, cell biology, and/or biochemistry. Send curriculum vitae and three letters of reference to: **Beth Levine, M.D., Howard Hughes Medical Institute, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX 75390-9113. E-mail: cindy.jozefiak@utsouthwestern.edu; laboratory website: http://www4.utsouthwestern.edu/idlabs/Levine/Levine_intro.htm.**

HHMI and UTSW are Equal Opportunity/Affirmative Action Employers.

WYSS TECHNOLOGY DEVELOPMENT FELLOWS

The Wyss Institute for Biologically Inspired Engineering at Harvard University ([website: http://www.wyss.harvard.edu](http://www.wyss.harvard.edu)) invites nominations of individuals of outstanding talent and technical skills for a number of Wyss Technology Development Fellow positions. Wyss Fellows will be provided with a competitive salary and additional funds to support independent exploratory research. The Fellowships are intended for brilliant young women and men of great promise with outstanding technical expertise who have completed their doctoral degree within the past five years. Fellowships are awarded for up to three years.

Although Wyss Fellows will be granted more independence and a greater emphasis on technology creation and translation than other postdoctoral appointees on campus, they can benefit from the role of Institute Core Faculty and members of the Advanced Technology Team as mentors.

A background in synthetic biology, living materials, or biological control is required. Candidates are specifically sought for the following enabling technology platforms: adaptive architecture and robotics; anticipatory medical devices; biomaterials evolution; biomimetic microsystems; and programmable nanomaterials. More information on these platforms can be found at our [website: http://www.wyss.harvard.edu](http://www.wyss.harvard.edu).

Interested applicants can obtain more information about the application process and can download the nomination sheet on the Wyss Institute [website: http://www.wyss.harvard.edu/viewpage/150/wyss-fellowship](http://www.wyss.harvard.edu/viewpage/150/wyss-fellowship). Applications should be sent to **e-mail: wyssfellow@wyss.harvard.edu.**

Harvard University is an Equal Opportunity/Affirmative Action Employer and applications from women and minority candidates are strongly encouraged.

Get your
career questions
answered.
**Careers
Forum**

Science Careers

From the journal *Science* **MAAS**

www.ScienceCareers.org



POSTDOCTORAL POSITIONS

Available in the Vascular Biology Center at the Medical College of Georgia

Medical College of Georgia (MCG) is located in the growing and thriving city of Augusta, recently ranked second most favorable place to live in Georgia.

In addition to being a magnet for world-class researchers, Augusta offers affordable living, high-quality schooling, and a rich culture and is within an easy three-hour drive of Atlanta, the Atlantic Ocean, and the mountains.

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A Ph.D. in a related field is required as is a background in synthetic biology, living materials, or biological control. Candidates are specifically sought for the following enabling technology platforms: adaptive architecture and robotics; anticipatory medical devices; biomaterials evolution; biomimetic microsystems; and programmable nanomaterials. For more specific information, please visit our [website: http://www.wyss.harvard.edu](http://www.wyss.harvard.edu).

Applications, assembled as single PDF files, should contain curriculum vitae, a cover letter describing research interests and goals, a full list of publications, copies of up to three relevant scientific papers, and names and contact information for at least three writers of letters of recommendation, who might be contacted as references. Applications should be sent to **e-mail: postdocs@wyss.harvard.edu.**

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